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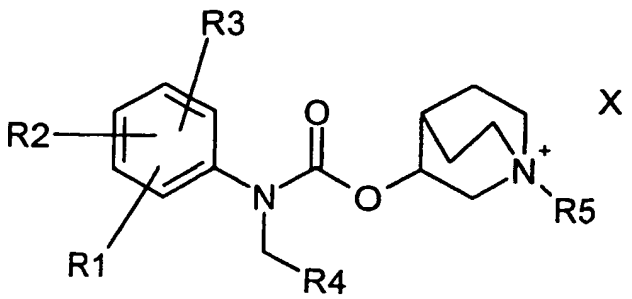
(54) Title: 1-ALKYL-1AZONIABICYCLO[2.2.2]OCTANE CARBAMATE DERIVATIVES



(I)

(57) Abstract: Carbamate of general formula (I), wherein R1, R2 and R3 are H, OH, NO_2, SH, CN, F, Cl, Br, I, COOH, $CONH_2$, $(C_1$-$C_4)$-alkoxycarbonyl, $(C_1$-$C_4)$-alkylsulfanyl, $(C_1$-$C_4)$-alkylsulfinyl, $(C_1$-$C_4)$-alkylsulfonyl, $(C_1$-$C_4)$-alkoxyl optionally substituted with one or several F, and $(C_1$-$C_4)$-alkyl optionally substituted with one or several F or OH; R4 is cycloalkyl, phenyl, heteroaryl or a bicyclic ring system; R5 is cycloalkyl, $(C_5$-$C_{10})$-alkyl, a substituted $(C_1$-$C_{10})$-alkyl; and X^- is a physiologically acceptable anion. Carbamate (I) is selective M_3 receptor antagonists versus M_2 receptor and may be used for the treatment of urinary incontinence (particularly, the one caused by overactive bladder), irritable bowel syndrome, and respiratory disorders (particulary, chronic obstructive pulmonary disease, chronic bronchitis, asthma, emphysema, and rhinitis), as well as in ophthalmic interventions.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

1-Alkyl-1-azoniabicyclo[2.2.2]octane carbamate derivatives

The present invention relates to novel compounds of type 3-alkylphenylcarbamoyloxy-1-alkyl-1-azoniabicyclo[2.2.2]octane, acting as muscarinic receptor antagonists, to the preparation of such compounds, and to the use of the same in the prevention and treatment of diseases related with respiratory tract, digestive tract, and urinary system.

BACKGROUND OF THE ART

It is known that compounds having a muscarinic receptor antagonist effect induce bronchodilation, gastrointestinal motility inhibition, gastric acid secretion reduction, dry mouth, mydriasis, tachycardia, as well as urinary bladder contraction inhibition.

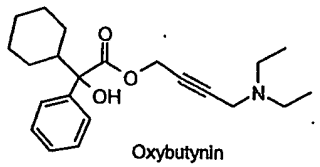
Between 1983 and 1993, continuous advances were produced in the knowledge of muscarinic receptor pharmacology. During this period, a total of five human genes codifying muscarinic receptor subtypes (m1, m2, m3, m4 and m5) were cloned and expressed, which encoded five functional receptors (M_1, M_2, M_3, M_4 and M_5).

The M_1 receptor is a postsynaptic neuronal receptor mainly located in brain and peripheral parasympathetic glands. In smooth cardiac muscle there is a major population of M_2 receptors. The M_3 receptor is predominantly located in glandular exocrine tissues such as salivary glands. The M_4 receptor is mainly present in cerebral cortex, striatum and some peripheral locations in specific species. The M_5 receptor has been described in the cerebral vessels. In the smooth muscle of intestinal tract, urinary bladder and bronchus, M_2 and M_3 receptors coexist. Nevertheless, functional information commonly accepted indicates that the M_3 receptor is the responsible for the contractile effect of the endogenous neurotransmitter in the last three tissues.

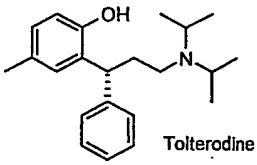
Few M_3 antagonists lacking M_2 affinity have been developed. The present invention contributes to fill this need by providing this kind of antagonists.

It seems interesting to obtain M_3 receptor selective antagonists to avoid the adverse effects due to blockade of other muscarinic receptors, mainly the cardiac effects due to M_2 receptor inhibition. At present, oxybutynin (Alza), trospium (Madaus) and tolterodine (Pharmacia), among others, are commercially available compounds showing reduced selectivity for M_2 and M_3 receptors. However, darifenacin (Pfizer), and solifenacin (Yamanouchi), both in clinical phase, exhibit M_3 antagonist activity with a reduced affinity towards M_2 receptor.

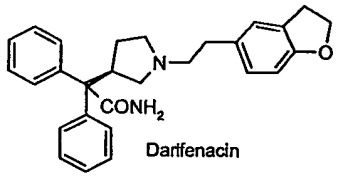
In contrast, tiotropium bromide (Böehringer Ingelheim) binds with similar affinity to muscarinic M_3 and M_2 receptors. However, it dissociates more slowly from M_3 than from M_2 receptors and subsequently has a long acting effect over M_3 receptor. In consequence, it may be considered as a functionally selective M_3 antagonist compound.



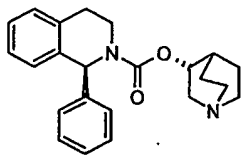
Oxybutynin



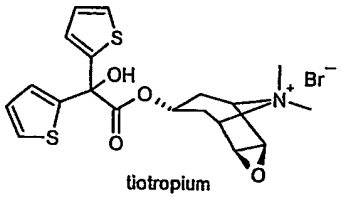
Tolterodine



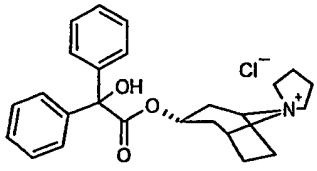
Darifenacin



solifenacin



tiotropium



trosplum

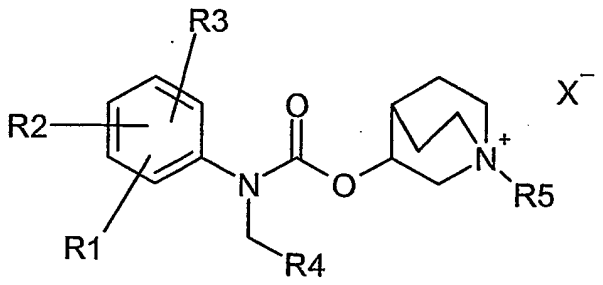
The following are some patent applications claiming compounds with carbamic structures as selective M_3 receptor antagonists: JP 04/95071, WO 9506635, EP 747355, EP 801067 and WO 0200652. All these documents describe carbamates different to those described in the present invention, and the later two describe the structurally nearest to the

hereby claimed. In document WO 0104118 some alkylquinuclidinium esters are described as selective antagonist for M_3 receptors, but they are also different from the compounds claimed in the present invention.

The compounds claimed in the present invention may be used either alone or in association with other therapeutic agents selected from the group consisting of: calcium channel blockers, α-adrenoceptor antagonists, β_2-agonists, dopamine agonists, corticosteroids, phosphodiesterase 4 inhibitors, leukotriene D4 antagonists, endothelin antagonists, substance-P antagonists, antitussives, decongestants, histamine H_1 antagonists, 5-lipooxigenase inhibitors, VLA-4 antagonists and theophylline.

SUMMARY OF THE INVENTION

An aspect of the present invention relates to the provision of new alkylquinuclidinium carbamates of general formula (I)



(I)

and prodrugs, individual isomers, racemic or non-racemic mixtures of isomers, pharmaceutically acceptable salts, polymorphs and solvates thereof,

wherein R1, R2 and R3 are radicals independently selected from the group consisting of H, OH, NO_2, SH, CN, F, Cl, Br, I, COOH, $CONH_2$, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylsulfanyl, (C_1-C_4)-alkylsulfinyl,

(C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkoxyl optionally substituted with one or several F, and, (C_1-C_4)-alkyl optionally substituted with one or several F or OH; alternatively, either R1 and R2, or R2 and R3 may be forming a biradical selected from the group consisting of -CH_2-CH_2-CH_2-, and -CH_2-CH_2-CH_2-CH_2-;

R4 is a radical selected from the group consisting of:

a) cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, norbornenyl, bicyclo[2.2.1]heptanyl, and 1-, 2-naphtyl, all of them optionally substituted with one or several substituents independently selected from the group consisting of OH, oxo (=O), SH, NO_2, CN, F, Cl, Br, I, $CONH_2$, COOH, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylsulfanyl, (C_1-C_4)-alkylsulfinyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkyl optionally substituted with one or several F or OH, and (C_1-C_4)-alkoxyl optionally substituted with one or several F;

b) a *C*-linked radical of a five or six membered heterocyclic ring containing at least one heteroatom selected from the group consisting of O, S, and N, being this heterocyclic ring optionally substituted with one or several substituents independently selected from the group consisting of OH, oxo (=O), SH, NO_2, CN, F, Cl, Br, I, $CONH_2$, COOH, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylsulfanyl, (C_1-C_4)-alkylsulfinyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkyl optionally substituted with one or several F or OH, and (C_1-C_4)-alkoxyl optionally substituted with one or several F;

c) a *C*-linked radical of a bicyclic ring system consisting of a phenyl ring fused to a five or six membered heterocyclic ring containing at least one heteroatom selected from the group consisting of O, S and N, being this bicyclic ring system optionally substituted with one or several substituents independently selected from the group consisting of OH, oxo (=O), SH, NO_2, CN, F, Cl, Br, I, $CONH_2$, COOH, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylsulfanyl, (C_1-C_4)-alkylsulfinyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkyl optionally substituted with one or several F or OH. and

(C_1-C_4)-alkoxyl optionally substituted with one or several F; and

d) phenyl optionally substituted with one or several substituents independently selected from the group consisting of OH, SH, NO_2, CN, F, Cl, Br, I, $CONH_2$, COOH, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylsulfanyl, (C_1-C_4)-alkylsulfinyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkyl optionally substituted with one or several F or OH, and (C_1-C_4)-alkoxyl optionally substituted with one or several F;

R5 is a radical selected from the group consisting of:

a) cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, all of them optionally substituted with one or several substituents independently selected from the group consisting of OH, oxo (=O), SH, NO_2, CN, F, Cl, Br, I, $CONH_2$, NR7CO-(C_1-C_4)-alkyl, COOH, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylsulfanyl, (C_1-C_4)-alkylsulfinyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkyl optionally substituted with one or several F or OH, and (C_1-C_4)-alkoxyl optionally substituted with one or several F;

b) (C_5-C_{10})-alkyl;

c) (C_1-C_{10})-alkyl substituted with one or several radicals independently selected from the group consisting of R6, COR6, NH_2, NR6R7, CONR6R7, NR7COR6, OH, OR6, COOR6, OCOR6, SO_2R6, SH, SR6, SOR6, COSR6, SCOR6, CN, F, Cl, Br, NO_2, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, norbornenyl, and bicyclo[2.2.1]heptanyl;

R6 is a radical selected from the group consisting of:

a) (C_1-C_5)-alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, norbornenyl, bicyclo[2.2.1]heptanyl, all of them optionally substituted with one or several substituents independently selected from the group consisting of OH, oxo (=O), SH, NO_2, CN, F, Cl, Br, I, $CONH_2$, NR7CO-(C_1-C_4)-alkyl, COOH, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylsulfanyl, (C_1-C_4)-alkylsulfinyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkyl optionally substituted with one or several F or OH, and (C_1-C_4)-alkoxyl optionally substituted with one or several F;

b) phenyl optionally substituted with one or several substituents independently selected from the group consisting of OH, SH, NO_2, CN, F, Cl, Br, I, $CONH_2$, NR7CO-(C_1-C_4)-alkyl, COOH, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylsulfanyl, (C_1-C_4)-alkylsulfinyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkyl optionally substituted with one or several F or OH, and (C_1-C_4)-alkoxyl optionally substituted with one or several F;

c) a *C*-linked radical of a five or six membered heterocyclic ring containing at least one heteroatom selected from the group consisting of O, S, and N, being this heterocyclic ring optionally substituted with one or several substituents independently selected from the group consisting of OH, oxo (=O), SH, NO_2, CN, F, Cl, Br, I, $CONH_2$, NR7CO-(C_1-C_4)-alkyl, COOH, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylsulfanyl, (C_1-C_4)-alkylsulfinyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkyl optionally substituted with one or several F or OH, and (C_1-C_4)-alkoxyl optionally substituted with one or several F; and

d) a *C*-linked radical of a bicyclic ring system consisting of a phenyl ring fused to a five or six membered heterocyclic ring containing at least one heteroatom selected from the group consisting of O, S and N, being this bicyclic ring system optionally substituted with one or several substituents independently selected from the group consisting of OH, oxo (=O), SH, NO_2, CN, F, Cl, Br, I, $CONH_2$, COOH, NR7CO-(C_1-C_4)-alkyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylsulfanyl, (C_1-C_4)-alkylsulfinyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkyl optionally substituted with one or several F or OH, and (C_1-C_4)-alkoxyl optionally substituted with one or several F;

R7 is a radical selected from the group consisting of H, phenoxycarbonyl, benzyloxycarbonyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylcarbonyl, (C_1-C_4)-alkylsulfonyl, and (C_1-C_5)-alkyl; and

X^- is a physiologically acceptable anion, such as chloride, bromide, iodide, hydroxide, sulfate, nitrate, phosphate, acetate, trifluoroacetate, fumarate, citrate, tartrate, oxalate, succinate, mandelate, methanesulfonate and *p*-

toluenesulfonate.

In a particular embodiment, R4 is 2-thiophene, 3-thiophene or phenyl, all of three cases optionally substituted with one or several substituents independently selected from the group consisting of OH, SH, NO_2, CN, F, Cl, Br, I, $CONH_2$, COOH, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylsulfanyl, (C_1-C_4)-alkylsulfinyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkyl optionally substituted with one or several F or OH, and (C_1-C_4)-alkoxyl optionally substituted with one or several F.

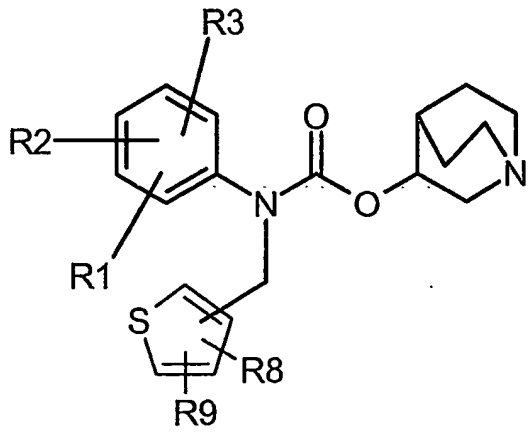
In another particular embodiment R5 is a (C_1-C_5)-alkyl substituted with one radical selected from the group consisting of R6, COR6, NR6R7, CONR6R7, NR7COR6, OR6, COOR6, OCOR6, SR6, SOR6, SO_2R6; and

R6 is a radical selected from the group consisting of:

a) phenyl optionally substituted with one or several substituents selected from the group consisting of OH, SH, CN, F, Cl, Br, I, $CONH_2$, COOH, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)alkylsulfanyl, (C_1-C_4)-alkylsulfinyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkyl optionally substituted with one or several F or OH, and (C_1-C_4)-alkoxyl optionally substituted with one or several F;

b) a *C*-linked radical of a five or six membered heterocyclic ring containing at least one heteroatom selected from the group consisting of O, S, and N, being this heterocyclic ring optionally substituted with one or several substituents independently selected from the group consisting of OH, SH, NO_2, CN, F, Cl, Br, I, $CONH_2$, COOH, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylsulfanyl, (C_1-C_4)-alkylsulfinyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkyl optionally substituted with one or several F or OH, and (C_1-C_4)-alkoxyl optionally substituted with one or several F.

Another aspect of the present invention relates to new intermediate compound of formula (X)



(X)

and prodrugs, individual isomers, racemic or non-racemic mixtures of isomers, pharmaceutically acceptable salts, polymorphs and solvates thereof,

for the preparation of a compound of formula (I) as defined in claim 1,

wherein R1, R2, R3, R8 and R9 are radicals independently selected from the group consisting of H, OH, NO_2, SH, CN, F, Cl, Br, I, $CONH_2$, COOH, $(C_1$-$C_4)$-alkoxycarbonyl, $(C_1$-$C_4)$-alkylsulfanyl, $(C_1$-$C_4)$-alkylsulfinyl, $(C_1$-$C_4)$-alkylsulfonyl, $(C_1$-$C_4)$-alkoxyl optionally substituted with one or several F, $(C_1$-$C_4)$-alkyl optionally substituted with one or several F or OH, except when R8 and R9 are H; alternatively, either R1 and R2, or R2 and R3 may be forming a biradical selected from the group consisting of $-CH_2$-CH_2-CH_2-, and $-CH_2$-CH_2-CH_2-CH_2-.

In still another particular embodiment of the present invention the configuration of the 3 position in the quinuclidine ring of all the preceding compounds is (*R*).

In cases where compounds of formula (I) have an asymmetric carbon, the racemic mixtures thereof may be resolved in their enantiomers by conventional methods, such as separation by column chromatography with chiral stationary phase or by fractioned crystallization of their diasteroisomeric salts. The later may be prepared by reaction with

enantiomerically pure acids or bases. Chiral compounds of formula (I) may also be obtained by enantioselective synthesis through chiral precursors.

The present invention also relates to physiologically acceptable salts of carbamates of general structure (I). In this specification "physiologically acceptable salts" means salts that are pharmaceutically acceptable, and that possess the desired pharmacological activity of the parent compound. Such salts include:

- Acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, nitric, sulfuric, and phosphoric acids, as well as with organic acids such as acetic, benzenesulfonic, benzoic, camphorsulfonic, mandelic, methanesulfonic, oxalic, succinic, fumaric, tartaric and maleic acids.
- Salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic or inorganic base. Acceptable organic bases include diethylamine, and triethylamine. Acceptable inorganic bases include aluminium hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate and sodium hydroxide.

It should be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) of the same acid addition salt.

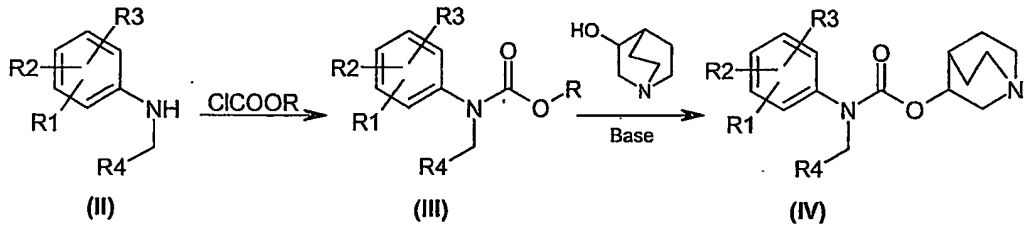
In this specification the terms 'alkyl' and 'alkoxyl' includes straight chained and branched structures.

Compounds of general structure (I) may be obtained from intermediates of general formula (IV), which may be prepared by three general methods (namely, A , B and C) represented in the scheme below.

Starting arylalkylamines (II) are commercially available, or may be obtained by known methods in the literature such as alkylation of anilines, reductive amination, or reduction of anilides.

According to Method A, acylation of the arylalkylamine (II) through a chloroformate (e.g. methylchloroformate, ethylchloroformate or 4-nitrophenylchloroformate) in an inert solvent [e.g. dimethylformamide (DMF), dichloromethane (DCM), 1,2-dichloroethane (1,2-DCE), tetrahydrofurane (THF) or toluene] is carried out first, at a temperature ranging from 0°C to the reflux temperature of the solvent. In some cases, it is advisable to carry out the reaction using the corresponding chloroformate as solvent, or using a base such as a tertiary amine or potassium carbonate. Then, the alkoxylic moiety is introduced by a transesterification reaction between the carbamate intermediate (III) and 3-quinuclidol, using a base such as sodium metal, sodium hydride, or sodium methoxide. The reaction may be carried out at a temperature ranging from 0°C to the reflux temperature of the solvent.

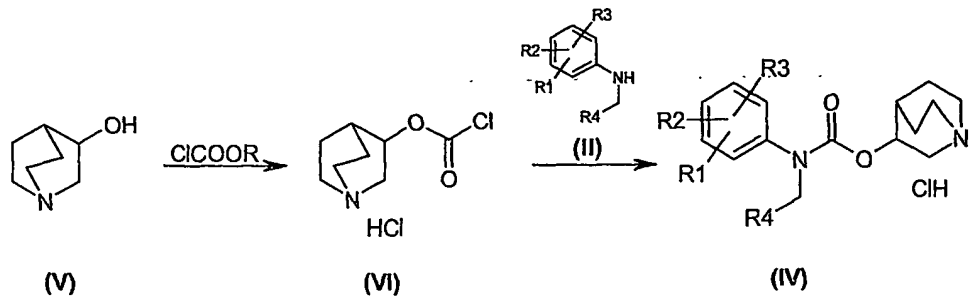
Method A



(II) (III) (IV)

According to Method B, 3-quinuclidol is first reacted with a chloroformate (e.g. trichloromethylchloroformate) in an inert solvent (e.g. DMF, DCM, 1,2-DCE) at a temperature ranging from 0°C to the reflux temperature of the solvent in order to obtain the corresponding hydrochloride of quinuclidol chloroformate. Then, arylalkylamine (II) is acylated with quinuclidol chloroformate. The reaction is carried out in an inert solvent (e.g. DMF, DCM, $CHCl_3$, 1,2-DCE) at a temperature ranging from 20°C to the reflux temperature of the solvent.

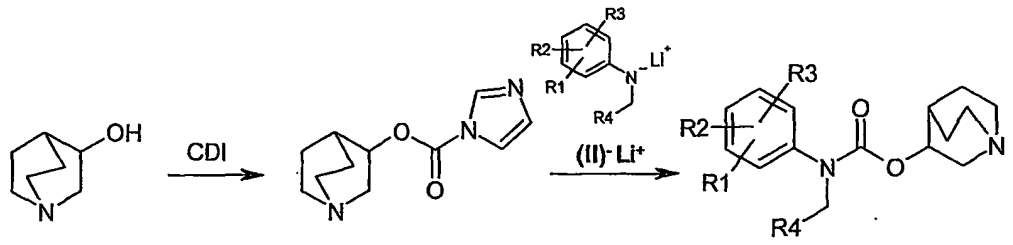
Method B



(V) (VI) (IV)

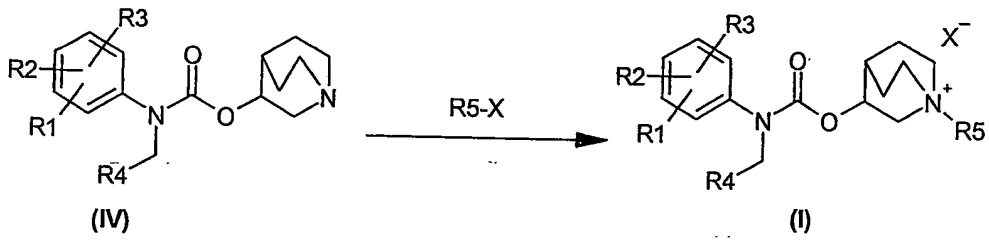
According to Method C, 3-quinuclidol is first reacted with a carbonyldiimidazole (DCI) in an inert solvent (e.g. DCM, 1,2-DCE) at room temperature in order to obtain the corresponding imidazole-1-carboxylic acid 1-azabicyclo[2.2.2]oct-3-yl ester. Then, arylalkylamine (II) is metalated in an inert solvent (e.g. THF) using BuLi and the ester was added at a temperature ranging from 0°C to room temperature.

Method C



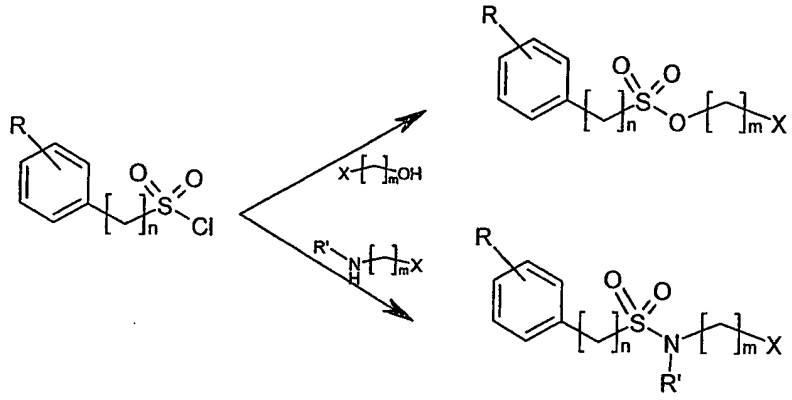
(V) (VII) (IV)

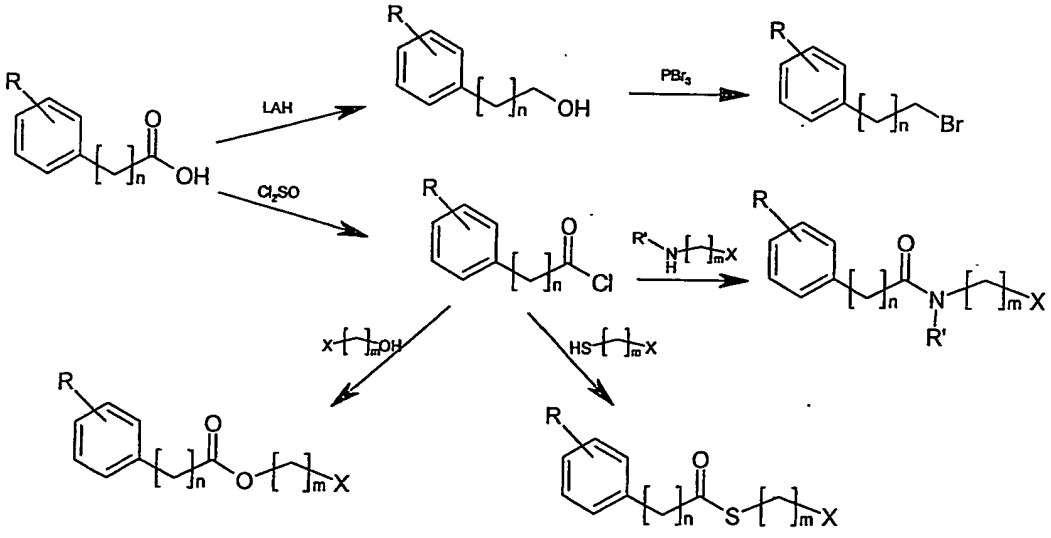
The quaternary ammonium salt of general formula (I), may be prepared by an *N*-alkylation reaction between an alkylating reagent (R5-X) and a compound of general formula (IV), using an inert solvent [e.g. DMF, DCM, $CHCl_3$, 1,2-DCE, CH_3CN (acetonitrile)] at a temperature ranging from 20°C to the reflux temperature of the solvent.

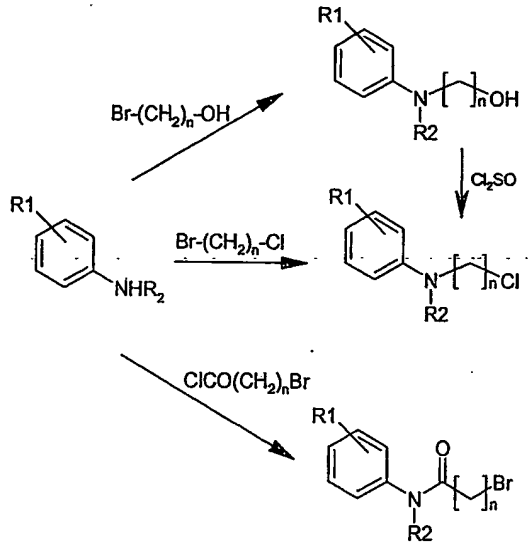


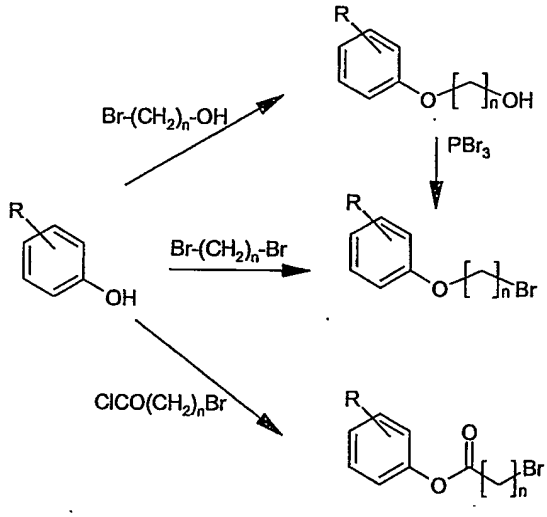
(IV) (I)

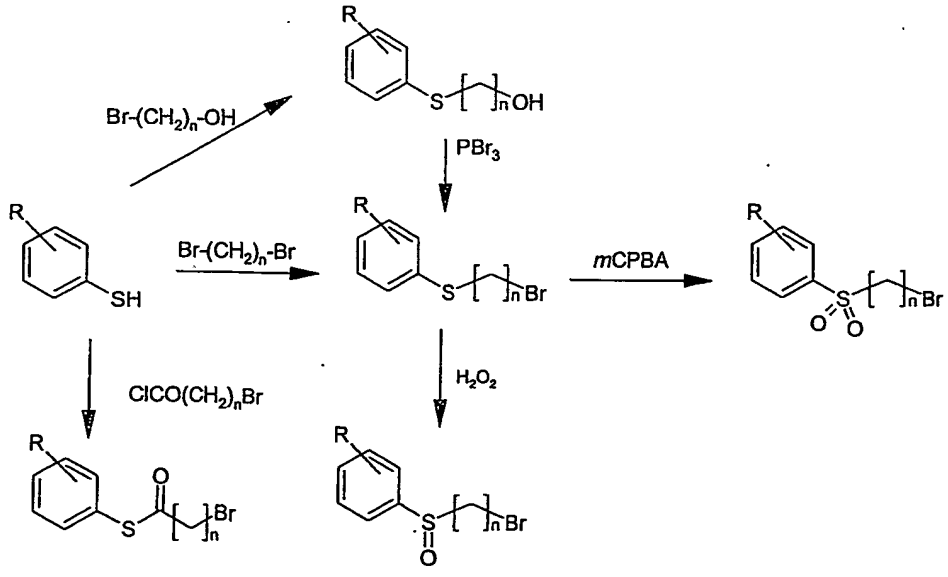
The R5-X compounds are either commercially available or may be prepared by known methods, such as those illustrated below.

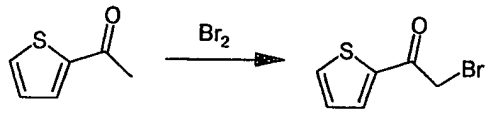




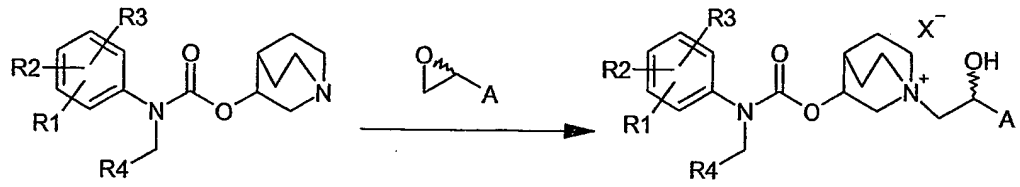

R1
Br-(CH2)n-OH
N
OH
R2
Cl2SO
R1
NHR2
Br-(CH2)n-Cl
R1
N
Cl
R2
ClCO(CH2)nBr
R1
O
N
Br
R2


R
Br-(CH2)n-OH
O
OH
PBr3
R
OH
Br-(CH2)n-Br
R
O
Br
ClCO(CH2)nBr
R
O
O
Br


R
Br-(CH2)n-OH
S
OH
PBr3
R
SH
Br-(CH2)n-Br
R
S
Br
mCPBA
R
O
S
O
Br
ClCO(CH2)nBr
H2O2
R
S
O
Br
R
S
O
Br



Additionally, when R5 is -CH_2-CHOH-A, wherein A is any radical except H, the quaternary amonium salt of general formula (I) may be prepared by alkylation between an epoxide and a compound of general formula (IV), in an inert solvent (e.g. DMF, DCM, $CHCl_3$, 1,2-DCE, CH_3CN) at a temperature ranging from 20°C to the reflux temperature of the solvent.



(IV) (I)

The compounds of the present invention are selective M_3 receptor antagonists *versus* M_2 receptor. For this reason they may be used for the treatment of urinary incontinence (particularly, the one caused by overactive bladder), irritable bowel syndrome, and respiratory disorders (particularly, chronic obstructive pulmonary disease, chronic bronchitis, asthma, emphysema, and rhinitis), as well as in ophthalmic interventions.

Thus, another aspect of the present invention is the use of carbamates of formula (I) for the preparation of medicaments for the treatment of the following diseases: urinary incontinence, particularly when it is caused by overactive bladder; irritable bowel syndrome; respiratory disorders, especially chronic obstructive pulmonary disease, chronic bronchitis, asthma, emphysema, and rhinitis. Furthermore, their use for the preparation of a medicament for ophthalmic interventions, is also forming part of this aspect of the invention.

<u>Binding test to human M_2 and M_3 muscarinic receptors</u>

The following tests show the M_3 antagonist activity of compounds of formula (I), as well as their selectivity towards the M_2 receptor. Some

results obtained for cloned human muscarinic M_2 and M_3 receptors are listed, and the used methodology is described.

Membranes from CHO-K1 cells transfected with human M_2 or M_3 receptors were used. The summarised experimental procedure for both receptors was the following: cell membranes (15-20 µg) were incubated with [^{3}H]-NMS (0.3-0.5 nM) for 60 min at 25 °C, in presence or absence of the antagonists. Incubation was carried out in 96 wells polystyrene microplates in a total incubation volume of 0.2 mL of PBS pH 7.4. Non specific binding was determined in parallel assays in presence of atropine (5 µM). Samples were filtered through type GF/C glass fibre, preincubated with PEI 0,3%. Filters were washed 3-4 times with 50 mM Tris-HCl, 0,9% NaCl, pH 7.4 at 4°C, and dried at 50 °C for 45 min. Filter bound radioactivity was quantified by liquid scintillation counting.

For the calculation of the inhibition constant (K_i), displacement curves were analysed by non-linear regression (GraphPad Prism). Dissociation constant (K_d) of [^{3}H]-NMS for each receptor was obtained through the saturation curves obtained in the same conditions as the experiments carried out with the corresponding antagonists. The results obtained, expressed as the mean of two independent experiments, each performed in duplicate, are shown in the table below. M_2/M_3 ratios greater than 1 indicates a M_3 selective activity.

	M_3 (k_i, nM)	M_2/M_3 (ratio)
OXYBUTYNIN	2.04	3
TOLTERODINE	10.20	1
DARIFENACIN	2.97	56
SOLIFENACIN	8.30	10
Int. 29	0.02	105
Int. 32	0.15	23
Ex. 11	0.34	80
Ex. 50	0.06	345
Ex. 69	0.02	32

EXAMPLES

The invention will be illustrated by the following non-limiting examples.

The structure of the different compounds was confirmed by ^{1}H-NMR, recorded using a Varian GEMINI-200 or Gemini-300 MHz instruments and chemical shifts are expressed as ppm (δ) from the internal reference TMS. The nomenclature used in this document is based on AUTONOM (**Auto**matic **Nom**enclature), a Beilstein Institute computerized system for the generation of IUPAC systematic nomenclature.

Intermediate 1: (*R*)-3-quinuclidyl chloroformate, hydrochloride

To a solution of 8.7 mL (74.8 mmol) of trichloromethyl chloroformate in 240 mL of dichloromethane, a solution of 4.75 g (37.4 mmol) of (*R*)-3-quinuclidol in 240 mL of dichloromethane was added dropwise at 0°C under inert atmosphere and with continuous stirring. Then, the mixture was stirred at room temperature for 24 h, and the solvent was distilled off under reduced pressure to give 8.46 g (37.4 mmol) of a white solid corresponding to the title compound. IR (KBr, cm^{-1}): 3380, 2650-2500, 1776.

Intermediate 2: (*R*)-Imidazole-1-Carboxylic acid 1-azabicyclo[2.2.2]oct-3-yl ester

To a suspension of 20.0 g (157 mmol) of (*R*)-3-quinuclidol in 400 mL of dichloromethane, 31.55 g (189 mmol) of DCI were added at room temperature. The yellow solution was stirred during 4 hrs under inert atmosphere. Then, 340 mL of water were added. The organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The obtained solid was crystallized with isopropyl acetate (IPAC)-heptane to give 23.5g (68%) of the title compound. IR (KBr, cm^{-1}): 1746.

Intermediate 3: (*R*)-Benzylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester hydrochloride

Method A

To a solution of 5.1 g (20 mmol) of benzylphenylcarbamic acid ethyl ester (Dannley, L. *J. Org. Chem.* **1957**, *22*, 268) and 7.63 g (60 mmol) of 3-quinuclidol in 120 mL of toluene, 800 mg (20 mmol) of sodium hydride (60% dispersion in oil) were added and the mixture was refluxed for three hours. During this time toluene was added to replace the distilled volume. The reaction crude was allowed to cool down, and was diluted with toluene (250 mL), washed with water and dried over anhydrous sodium sulfate. Then, the solvent was distilled off under reduced pressure. The obtained oil was treated at room temperature with hydrogen chloride saturated ethanol, the solvent was distilled off, and the obtained solid was broken up with a 1:1 ethyl acetate/diethyl ether mixture to give 230 mg (0.6 mmol) of a white solid corresponding to the title compound (m.p.: 54°C).

Method B

To a suspension of 750 mg (2.58 mmol) of 3-quinuclidyl chloroformate hydrochloride in 20 mL of 1,2-DCE, a solution of 395 mg (2.15 mmol) of *N*-phenylbenzylamine in 5 mL of 1,2-DCE was added dropwise. Once completed the addition, the mixture was refluxed for three hours. The reaction crude was allowed to cool down and the solvent distilled off under reduced pressure. The residue was purified by column chromatography (SiO_2, eluent: $CHCl_3$-methanol 10:1) yielding 720 mg (1.95 mmol) of a hygroscopic foam corresponding to the title compound. IR (KBr, cm^{-1}): 3400-3200, 2700-2300, 1700 cm^{-1}. ^{1}H-RMN ($CDCl_3$): 12.30 (s, 1H), 7.20-6.90 (m, 10H), 5.10 (m, 1H), 4.83 (m, 2H), 3.52 (m, 1H), 3.18 (m, 4H), 2.80 (m, 1H), 2.34 (s, 1H), 1.92 (m, 2H), 1.60 (m, 2H).

Method C

To a solution of 2.73 g (14.9 mmol) of *N*-phenylbenzylamine in 20 mL of THF, previously cooled at -10°C, 5.96 mL of *n*-BuLi (2.5 M) were added dropwise. At -10°C 3.29 g (14.9 mmol) of intermediate 2 in 35 mL of THF were slowly added. The resulting mixture was stirred for 2 h and allowed to rise room temperature, then 35 mL of water was added. The solution was extracted with ethyl acetate, and the organic phase was dried over

anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residue was dissolved in EtOH/HCl and the solvent evaporated again. The new residue was purified by column chromatography (eluent: chloroform-methanol 10:1) yielding 1.53 g of an hygroscopic foam corresponding to the title compound. IR (KBr, cm^{-1}): 3400-3200, 2700-2300, 1700 cm^{-1}.

The following intermediates (4 to 15) were prepared using method B, described in the patent application WO 0200652:

Intermediate 4: (*R*)-Benzyl-*m*-tolylcarbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride.
Intermediate 5: (*R*)-Benzyl-(3-fluorophenyl)carbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride.
Intermediate 6: (*R*)-(4-Fluorobenzyl)phenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride.
Intermediate 7: (*R*)-(4-Fluorobenzyl)-*m*-tolylcarbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride.
Intermediate 8: (*R*)-(4-Fluorobenzyl)-(2-fluorophenyl)carbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride.
Intermediate 9: (*R*)-(4-Fluorobenzyl)-(3-fluorophenyl)carbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride.
Intermediate 10: (*R*)-(3,4-Difluorobenzyl)phenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride.
Intermediate 11: (*R*)-(3,4-Difluorobenzyl)-*m*-tolylcarbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride.
Intermediate 12: (*R*)-(3,4-Difluorobenzyl)-(2-fluorophenyl)carbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride.
Intermediate 13: (*R*)-(3,4-Difluorobenzyl)-(3-fluorophenyl)carbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride.
Intermediate 14: (*R*)-(2-Fluorophenyl)-(3,4,5-trifluorobenzyl)carbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride.
Intermediate 15: (*R*)-(3-Fluorophenyl)-(3,4,5-trifluorobenzyl)carbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride.
Intermediate 16: (*R*)-3-Cyclohexylmethylphenylcarbamoyloxy-1-

azoniabicyclo[2.2.2]octane; hydrochloride

The following new intermediates were prepared using any of the methods described above:

Intermediate 17: (*R*)-Thiophen-2-ylmethyl-*m*-tolylcarbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester
^{1}H-NMR ($CDCl_3$): 7.25 (d, 1H), 7.22 (d, 1H), 7.06 (d, 1H), 6.94 (m, 1H), 6.91 (dd, 2H), 6.84 (dd, 1H), 4.95 (s, 2H), 4.88 (m, 1H), 3.32 (dd, 1H), 3.10-2.60 (m, 5H), 2.31 (s, 3H), 2.14 (m, 1H), 1.80-1.30 (m, 4H).

Intermediate 18: (*R*)-(2-Fluorophenyl)thiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester
^{1}H-NMR ($CDCl_3$): 7.35-7.20 (m, 2H), 7.15-7.00 (m, 3H), 6.86 (m, 2H), 4.95 (s, 2H), 4.82 (m, 1H), 3.22 (m, 1H), 3.15-2.50 (m, 5H), 2.01 (m, 1H), 1.80-1.50 (m, 2H), 1.45-1.20 (m, 2H).

Intermediate 19: (*R*)-(3-Fluorophenyl)thiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride
^{1}H-NMR ($CDCl_3$): 7.35-7.20 (m, 2H), 7.15-7.00 (m, 3H), 6.86 (m, 2H), 4.95 (s, 2H), 4.82 (m, 1H), 3.22 (m, 1H), 3.15-2.50 (m, 5H), 2.01 (m, 1H), 1.80-1.50 (m, 2H), 1.45-1.20 (m, 2H).

Intermediate 20: (*R*)-(3-Methylthiophen-3-ylmethyl)phenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride
^{1}H-NMR ($CDCl_3$): 11.69 (br, 1H), 7.29 (m, 3H), 7.17-6.90 (m, 3H), 6.71 (dd, 1H), 5.08 (m, 1H), 4.89 (s, 2H), 3.61 (m, 1H), 3.40-2.60 (m, 5H), 2.37 (m, 1H), 2.19-1.80 (m, 3H), 1.87 (s, 3H), 1.61 (m, 1H).

Intermediate 21: (*R*)-3-[(4-Bromothiophen-2-ylmethyl)phenylcarbamoyloxy]-1-azoniabicyclo[2.2.2]octane; hydrochloride
^{1}H-NMR ($CDCl_3$): 7.42-7.30 (m, 3H), 7.15 (d, 1H), 7.08 (br, 2H), 6.79 (d, 1H), 5,30 (br, 1H), 5.04 (m, 1H), 4.90 (s, 2H), 3.55-3.40 (m, 1H), 3.20-2.95 (m, 4H), 2.80 (br, 1H), 2.32 (m, 1H), 2.00-1.65 (m, 2H), 1.59 (m, 2H).

Intermediate 22: (*R*)-(5-Methylthiophen-2-ylmethyl)phenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride

^{1}H-NMR ($CDCl_3$): 12.20 (br, 1H), 7.40-7.28 (m, 3H), 7.16-6.90 (br, 2H), 6.59 (d, 1H), 6.53 (d, 1H), 5.09 (m, 1H), 4.85 (s, 2H), 3.53 (br, 1H), 3.35-3.00 (m, 4H), 2.82 (br, 1H), 2.45 (s, 3H), 2.39 (m, 1H), 2.10-1.55 (m, 4H).

Intermediate 23: (*R*)-(5-Chlorothiophen-2-ylmethyl)-(2-fluorophenyl)carbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride

^{1}H-NMR ($CDCl_3$): 7.40-7.27 (m, 1H), 7.23-7.05 (m, 3H), 6.71 (d, 1H), 6.60 (d, 1H), 5.07 (m, 1H), 4.81 (s, 2H), 3.49 (m, 1H), 3.30-3.00 (m, 4H), 2.87 (m, 1H), 2.39 (m, 1H), 2.00-1.80 (m, 2H), 1.75-1.53 (m, 2H).

Intermediate 24: (*R*)-(5-Bromothiophen-2-ylmethyl)phenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride

^{1}H-NMR ($CDCl_3$): 7.42-7.29 (m, 3H), 7.12-7.00 (m, 2H), 6.86 (d, 1H), 6.59 (d, 1H), 5.30 (br, 1H), 5.04 (m, 1H), 4.86 (s, 2H), 3.50-3.35 (m, 1H), 3.20-2.90 (m, 4H), 2.80 (br, 1H), 2.32 (m, 1H), 2.00-1.65 (m, 3H), 1.59 (m, 1H).

Intermediate 25: (*R*)-(5-Bromothiophen-2-ylmethyl)-*m*-tolylcarbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride

^{1}H-NMR ($CDCl_3$): 7.21 (d, 1H), 7.11 (d, 1H), 6.95-6.80 (m, 2H), 6.86 (d, 1H), 6.60 (d, 1H), 5.03 (m, 1H), 4.84 (s, 2H), 3.50-3.35 (m, 1H), 3.20-2.95 (m, 4H), 2.80 (br, 1H), 2.34 (m, 1H), 2.34 (s, 3H), 2.00-1.60 (m, 4H).

Intermediate 26: (*R*)-(3-Fluorophenyl)thiophen-3-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride

^{1}H-NMR ($CDCl_3$): 8.14 (br, 1H), 7.38-7.24 (m, 2H), 7.08 (d, 1H), 6.99-6.92 (m, 4H), 5.07 (m, 1H), 4.81 (s, 2H), 3.65 (ddd, 1H), 3.27-3.08 (m, 4H), 2.90 (q, 1H), 2.31 (m, 1H), 2.10-1.80 (m, 2H), 1.70-1.55 (m, 2H).

Intermediate 27: (*R*)-(2-Fluorophenyl)-(3-methylthiophen-2-ylmethyl)carbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride

^{1}H-NMR ($CDCl_3$): 7.31 (m, 1H), 7.13 (d, 1H), 7.10-6.92 (m, 2H), 7.07 (d, 1H), 6.72 (d, 1H), 5.11 (m, 1H), 4.87 (m, 2H), 3.51 (m, 1H), 3.35-2.98 (m, 4H), 2.85 (m, 1H), 2.42 (m, 1H), 1.93 (s, 3H), 2.10-1.50 (m, 4H).

Intermediate 28: (*R*)-(2-Fluorophenyl)-(5-methylthiophen-2-ylmethyl)carbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride
^{1}H-NMR ($CDCl_3$): 7.31 (m, 1H), 7.20-7.04 (m, 3H), 6.59 (d, 1H), 6.53 (dd, 1H), 5.09 (m, 1H), 4.80 (m, 2H), 3.53 (m, 1H), 3.37-3.00 (m, 4H), 2.86 (br, 1H), 2.45 (s, 3H), 2.44 (m, 1H), 2.10-1.55 (m, 4H).

Intermediate 29: (*R*)-(5-Chlorothiophen-2-ylmethyl)-(3-fluorophenyl)carbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride
^{1}H-NMR ($CDCl_3$): 7.34 (td, 1H), 7.04 (td, 1H), 6.95-6.78 (m, 2H), 6.73 (d, 1H), 6.62 (d, 1H), 5.09 (m, 1H), 4.83 (s, 2H), 3.52 (m, 1H), 3.35-3.05 (m, 4H), 2.93 (br, 1H), 2.41 (m, 1H), 2.10-1.55 (m, 4H).

Intermediate 30: (*R*)-(5-Ethylthiophen-2-ylmethyl)-*m*-tolylcarbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride
^{1}H-NMR ($CDCl_3$): 7.40-7.28 (m, 3H), 7.15-7.02 (m, 2H), 6.61 (d, 1H), 6.57 (d, 1H), 5.12 (m, 1H), 4.87 (s, 2H), 3.55-3.35 (m, 1H), 3.20-2.95 (m, 4H), 2.80 (q, 2H), 2.80-2.70 (m, 1H), 2.35 (m, 1H), 2.00-1.55 (m, 4H), 1.28 (t, 3H).

Intermediate 31: (*R*)-Phenylthiophen-3-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride
^{1}H-NMR ($CDCl_3$): 7.35-7.24 (m, 4H), 7.12-6.92 (m, 2H), 7.03 (d, 1H), 6.96 (dd, 1H), 5.01 (m, 1H), 4.77 (s, 2H), 3.48 (ddd, 1H), 3.25-2.97 (m, 4H), 2.80 (m, 1H), 2.27 (m, 1H), 2.01-1.77 (m, 2H), 1.65-1.45 (m, 2H).

Intermediate 32: (*R*)-Thiophen-3-ylmethyl-*m*-tolylcarbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride
^{1}H-NMR ($CDCl_3$): 7.27 (dd, 1H), 7.18 (t, 1H), 7.06 (d, 1H), 7.04 (s, 1H), 6.97 (dd, 1H), 6.82 (br, 2H), 5.03 (m, 1H), 4.76 (s, 2H), 3.50 (m, 1H), 3.28-2.98 (m, 4H), 2.83 (m, 1H), 2.30 (s, 3H), 2.30 (m, 1H), 2.05-1.75 (m, 2H), 1.70-1.50 (m, 2H).

Intermediate 33: (*R*)-(2-Fluorophenyl)thiophen-3-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride

^{1}H-NMR ($CDCl_3$): 7.38-7.20 (m, 2H), 7.11 (d, 1H),7.10-6.95 (m, 2H), 7.05 (s, 1H), 6.99 (dd, 1H), 5.02 (m, 1H), 4.78 (dd, 2H), 3.48 (m, 1H), 3.30-2.95 (m, 4H), 2.83 (m, 1H), 2.29 (m, 1H), 2.05-1.80 (m, 2H), 1.70-1.50 (m, 2H).

The following new intermediates were also prepared using any of the methods described above, and they have been identified by ^{1}H-NMR:

(*R*)-(3-Fluorophenyl)-(3-methylthiophen-2-ylmethyl)carbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride

(*R*)-3-(4-Bromothiophen-2-ylmethyl)-*m*-tolylcarbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride

(*R*)- (4-Bromothiophen-2-ylmethyl)-(2-fluorophenyl)carbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride

(*R*)-(4-Bromothiophen-2-ylmethyl)-(3-fluorophenyl)carbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride

(*R*)-(3-Fluorophenyl)-(5-methylthiophen-2-ylmethyl)carbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride

(*R*)-(5-Chlorothiophen-2-ylmethyl)phenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride

(*R*)-(5-Bromothiophen-2-ylmethyl)-(2-fluorophenyl)carbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride

(*R*)-(5-Bromothiophen-2-ylmethyl)-(3-fluorophenyl)carbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride

(*R*)-(5-Ethylthiophen-2-ylmethyl)phenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride

(*R*)-(5-Ethylthiophen-2-ylmethyl)-(2-fluorophenyl)carbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride

(*R*)-(5-Ethylthiophen-2-ylmethyl)-(3-fluorophenyl)carbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester; hydrochloride

Example 1: (*R*)-3-(Benzylphenylcarbamoyloxy)-1-Cyclopropyl-1-azoniabicyclo[2.2.2]octane; bromide

200 mg (0.59 mmol) of Intermediate 3 and 0.47 mL of bromocyclopropane (0.59 mmol) were mixed in 5 mL of acetonitrile/chloroform (2:3). The resulting solution was refluxed for 12 hours. The solvent was evaporated and the residue purified by column chromatography [SiO_2, eluent: dichloromethane-methanol (20:1)] to yield 130 mg (47%) of an hygroscopic white solid, corresponding to the title compound. ^{1}H-NMR ($CDCl_3$): 7.27 (m, 10H), 4.87 (m, 2H), 4.80 (m, 1H), 3.18 (ddd, 1H), 3.01 (m, 1H), 2.80-2.50 (m, 5H), 2.23 (m, 1H), 1.98 (m, 2H), 1.65-1.18 (m, 6H).

The following compounds were synthesised according to Example 1:

Example 2: (*R*)-3-(Benzylphenylcarbamoyloxy)-1-(2-Chlorobenzyl)-1-azoniabicyclo[2.2.2]octane; chloride

The yield was 131 mg (45%) as a yellow oil. IR (film, cm^{-1}): 1694. ^{1}H-NMR ($CDCl_3$): 7.60-7.16 (m, 14H), 5.03 (m, 1H), 4.92 (dd, 2H), 4.80 (s, 2H), 4.10 (m, 1H), 3.77 (m, 3H), 3.35 (m. 1H), 2.78 (m, 1H), 2.28 (m, 1H), 1.98 (m, 2H), 1.78 (m, 1H), 1.60 (m, 1H).

Example 3: (*R*)-3-(Benzylphenylcarbamoyloxy)-1-(5-methylsulfanyl-[1,3,4]thiadiazol-2-ylsulfanylmethyl)-1-azoniabicyclo[2.2.2]octane; chloride;

The yield was 77 mg (53%) as white solid. ^{1}H-NMR ($CDCl_3$): 7.27-7.18 (m, 10H), 6.97 (t, 2H), 6.82 (dd, 2H), 5.12 (dd, 1H), 4.82 (m, 2H), 4.34 (s, 2H), 4.30-4.05 (m, 3H), 4.05-3.70 (m, 4H), 3.05 (dd, 1H), 2.33 (m, 1H), 2.10-1.50 (m, 4H).

Example 4: (*R*)-3-(Benzylphenylcarbamoyloxy)-1-ethoxycarbonylmethyl-1-azoniabicyclo[2.2.2]octane; bromide

The yield was 60 mg (35%) as a oil. IR (film, cm^{-1}): 1743, 1701. ^{1}H-NMR ($CDCl_3$): 7.28 (m, 10H), 5.15-4.80 (m, 5H), 4.40-3.50 (m, 8H), 2.38 (m, 1H), 2.01 (m, 2H), 1.78 (m, 1H), 1.58 (m, 1H), 1.29 (t, 3H).

Example 5: (*R*)-3-(Benzyl-*m*-tolylcarbamoyloxy)-1-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]-1-azoniabicyclo[2.2.2]octane; bromide

The yield was 120 mg (25%) as white solid. IR (film, cm^{-1}): 1694. ^{1}H-NMR ($CDCl_3$): 7.30-6.80 (m, 11H), 6.62 (d, 1H), 5.16 (m, 1H), 4.77 (m, 2H), 4.48 (t, 2H), 4.21 (m, 1H), 3.90-3.40 (m, 6H), 3.09 (t, 2H), 2.88 (m, 3H), 2.29 (s, 3H), 2.01-1.40 (m, 5H).

Example 6: (*R*)-3-[Benzyl-(3-fluorophenyl)carbamoyloxy]-1-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]-1-azoniabicyclo[2.2.2]octane; bromide
The yield was 51 mg (16%) as white solid. IR (film, cm^{-1}): 1705. ^{1}H-NMR ($CDCl_3$): 7.30-6.90 (m, 10H), 6.80 (d, 1H), 6.68 (d, 1H), 5.17 (m, 1H), 4.90 (m, 2H), 4.52 (t, 2H), 4.16 (m, 1H), 3.90-3.60 (m, 5H), 3.41 (m, 1H), 3.13 (t, 2H), 2.88 (m, 3H), 2.21-1.60 (m, 5H).

Example 7: (*R*)-3-[(4-Fluorobenzyl)phenylcarbamoyloxy]-1-(2-*m*-tolylethyl)-1-azoniabicyclo[2.2.2]octane; bromide
The yield was 110 mg (42%) as a yellow solid. ^{1}H-NMR ($CDCl_3$): 7.40-7.00 (m, 10H), 7.09 (s, 1H), 6.98 (t, 2H), 5.09 (m, 1H), 4.78 (m, 2H), 4.13 (m, 1H), 4.00-3.60 (m, 5H), 3.30 (br, 1H), 2.95 (br, 1H), 2.93 (t, 2H), 2.33 (m, 1H), 2.30 (s, 3H), 2.10-1.70 (m, 3H), 1.61 (m, 1H).

Example 8: (*R*)-1-[2-(4-Ethoxyphenyl)ethyl]-3-[(4-fluorobenzyl)phenylcarbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide
The yield was 106 mg (38%) as white solid. ^{1}H-NMR ($CDCl_3$): 7.40-6.95 (m, 11H), 6.79 (d, 2H), 5.06 (m, 1H), 4.78 (m, 2H), 4.15-3.60 (m, 6H), 3.95 (q, 2H), 3.35 (br, 1H), 3.05 (br, 1H), 2.93 (t, 2H), 2.32 (m, 1H), 2.10-1.70 (m, 4H), 1.38 (t, 3H).

Example 9: (*R*)-3-[(4-Fluorobenzyl)phenylcarbamoyloxy]-1-[2-(4-nitrophenyl)ethyl]-1-azoniabicyclo[2.2.2]octane; bromide
The yield was 72 mg (26%) as yellow solid. ^{1}H-NMR ($CDCl_3$): 8.04 (d, 2H), 7.59 (d, 2H), 7.40-7.03 (m, 7H), 6.98 (t, 2H), 5.11 (m, 1H), 4.79 (m, 2H), 4.25 (m, 1H), 4.05 (m, 1H), 3.95-3.70 (m, 4H), 3.55 (br, 1H), 3.16 (t, 2H), 3.05 (br, 1H), 2.93 (t, 2H), 2.32 (m, 1H), 2.10-1.50 (m, 4H).

Example 10: (*R*)-1-[2-(2,4-Difluorophenylsulfanyl)ethyl]-3-[(4-

fluorobenzyl)phenylcarbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide
The yield was 182 mg (64%) as yellow solid. ^{1}H-NMR ($CDCl_3$): 7.61 (ddd, 1H), 7.40-7.17 (m, 6H), 7.09 (m, 1H), 7.00-6.88 (m, 2H), 6.97 (t, 1H), 6.82 (dd, 1H), 5.11 (m, 1H), 4.78 (s, 2H), 4.23 (ddd, 1H), 4.00-3.50 (m, 5H), 3.45-3.20 (m, 3H), 2.93 (br, 1H), 2.32 (m, 1H), 2.10-1.80 (m, 3H) 1.60 (m, 1H).

Example 11: (*R*)-3-[(4-Fluorobenzyl)phenylcarbamoyloxy]-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; bromide
The yield was 32 mg (10%) as white solid. IR (film, cm^{-1}): 1703. ^{1}H-NMR ($CDCl_3$): 7.40-6.80 (m, 12H), 6.85 (d, 2H), 5.13 (m, 1H), 4.88 (m, 2H), 4.18 (m, 1H), 4.05 (t, 2H), 3.90-3.60 (m, 4H), 3.47 (m, 1H), 3.23 (m, 1H), 2.80 (m, 1H), 2.40-1.80 (m, 7H).

Example 12: (*R*)- 1-Cyclobutylmethyl-3-[(4-fluorobenzyl)-*m*-tolylcarbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide
The yield was 132 mg (63%) as an oil. ^{1}H-NMR ($CDCl_3$): 7.25-7.17 (m, 3H), 7.06 (d, 2H), 7.00 (d, 2H), 6.88 (br, 1H), 5.09 (m, 1H), 4.78 (m, 2H), 4.10-3.80 (m, 3H), 3.56 (d, 2H), 3.55 (m, 1H), 3.05 (br, 1H), 2.75 (br, 1H), 2.35 (m, 1H), 2.32 (s, 3H), 2.10-0.90 (m, 11H).

Example 13: (*R*)-1-[2-(3,4-Dimethoxyphenyl)ethyl]-3-[(4-fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide
The yield was 190 mg (60%) as a white solid. ^{1}H-NMR ($CDCl_3$): 7.35-6.92 (m, 10H), 6.76 (s, 2H), 5.08 (m, 1H), 4.78 (s, 2H), 4.25-3.60 (m, 6H), 3.95 (s, 3H), 3.82 (s, 3H), 3.26 (m, 1H), 2.97 (m, 3H), 2.30 (m, 1H), 2.10-1,50 (m, 4H).

Example 14: (*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[2-(4-methoxyphenyl)-2-oxoethyl]-1-azoniabicyclo[2.2.2]octane; bromide
The yield was 47 mg (19%) as a yellow solid. ^{1}H-NMR ($CDCl_3$): 8.11 (d, 2H), 7.30-6.87 (m, 10H), 5.80-5.50 (m, 2H), 5.15 (m, 1H), 4.78 (m, 2H), 4.53 (m, 1H), 4.35-3.90 (m, 3H), 3.82 (s, 3H), 3.55 (m, 1H), 2.86 (m, 1H), 2.45-1.80 (m, 4H), 1.60 (m, 1H).

Example 15: (*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[2-oxo-2-(1*H*-pyrrol-2-yl)ethyl]-1-azoniabicyclo[2.2.2]octane; bromide
The yield was 90 mg (55%) as a brown solid. ^{1}H-NMR ($CDCl_3$): 7.35-7.00 (m, 9H), 6.97 (t, 2H), 5.30 (m, 2H), 5.11 (m, 1H), 4.76 (m, 2H), 4.43 (m, 1H), 4.10-3.80 (m, 4H), 3.49 (m, 1H), 3,20 (br, 1H), 2.33 (m, 1H), 2.10-1.55 (m, 4H).

Example 16: (*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-(2-oxo-2-thiophen-2-ylethyl)-1-azoniabicyclo[2.2.2]octane; bromide
The yield was 101 mg (60%) as a yellow solid. ^{1}H-NMR ($CDCl_3$): 8.39 (d, 2H), 7.73 (d, 1H), 7.30-7.18 (m, 3H), 7.13 (s, 1H), 7.10-7.05 (m, 3H), 6.97 (t, 2H), 5.71 (dd, 2H), 5.15 (m, 1H), 4.78 (dd, 2H), 4.51 (m, 1H), 4.35-3.90 (m, 4H), 3.56 (m, 1H), 2.35 (m, 1H), 2.45-1.55 (m, 4H).

Example 17: (*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-(3-methoxyphenoxycarbonylmethyl)-1-azoniabicyclo[2.2.2]octane; bromide
The yield was 43 mg (24%) as a yellow solid. ^{1}H-NMR ($CDCl_3$): 7.35-7.16 (m, 7H), 7.13-7.00 (m, 3H), 6.97 (t, 2H), 5.21-4.90 (m, 3H), 4.85 (d, 1H), 4.76 (d, 1H), 4.41 (m, 1H), 4.25-3.60 (m, 4H), 3.76 (s, 3H), 3.53 (m, 1H), 2.35 (m, 1H), 2.20-1.70 (m, 3H), 1.60 (m, 1H).

Example 18: (*R*)-1-Cyclopentylcarbamoylmethyl-3-[(4-fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide
The yield was 100 mg (39%) as a brown solid. ^{1}H-NMR ($CDCl_3$): 8.78 (m, 1H), 7.35-7.00 (m, 6H), 6.97 (t, 2H), 5.11 (m, 1H), 4.78 (s, 2H), 4.61 (d, 1H), 4.30-3.85 (m, 4H), 4.23 (d, 1H), 3.80-3.60 (m, 3H), 3.21 (m, 1H), 2.37 (m, 1H), 2.10-1.40 (m, 12H).

Example 19: (*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[(2-fluorophenylcarbamoyl)methyl]-1-azoniabicyclo[2.2.2]octane; bromide
The yield was 93 mg (60%) as a brown solid. ^{1}H-NMR ($CDCl_3$): 10.23 (br, 1H), 7.73 (td, 1H), 7.40-6.98 (m, 9H), 6.94 (t, 2H), 5.15 (m, 1H), 5.01 (d, 1H), 4.79 (s, 2H), 4.72 (d, 1H), 4.45 (m, 1H), 4.30-3.70 (m, 4H), 3.39 (m, 1H), 2.38 (m, 1H), 2.10-1.60 (m, 4H).

Example 20: (*R*)-1-[2-(4-acetylaminophenylsulfanyl)ethyl]-3-[(4-fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide

The yield was 30 mg (9%) as a yellow solid. ^{1}H-NMR ($CDCl_3$): 9.52 (s, 1H), 7.63 (d, 2H), 7.40-6.94 (m, 9H), 5.10 (m, 1H), 4.73 (s, 2H), 4.30-4.00 (m, 2H), 3.95-3.60 (m, 4H), 3.40-3.20 (m, 3H), 2.90 (m, 1H), 2.35 (m, 1H), 2.19 (s, 3H), 2.10-1.50 (m, 4H).

Example 21: (*R*)-1-[2-(2,3-Dimethylphenylsulfanyl)ethyl]-3-[(4-fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide

The yield was 94 mg (59%) as a yellow solid. ^{1}H-NMR ($CDCl_3$): 7.35-7.00 (m, 9H), 6.96 (t, 2H), 5.11 (m, 1H), 4.76 (s, 2H), 4.25-3.90 (m, 3H), 3.85-3.40 (m, 3H), 3.40-3.10 (m, 3H), 2.86 (m, 1H), 2,35 (s, 3H), 2.33 (m, 1H), 2.30 (s, 3H), 2.20-1.50 (m, 4H).

Example 22: (*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[2-(1-methyl-1*H*-imidazol-2-ylsulfanyl)ethyl]-1-azoniabicyclo[2.2.2]octane; chloride

The yield was 79 mg (49%) as a brown oil. ^{1}H-NMR ($CDCl_3$): 7.67 (d, 1H), 7.32-7.05 (m, 6H), 6.97 (t, 2H), 6.73 (d, 1H), 5.13 (m, 1H), 4.77 (s, 2H), 4.65 (m, 2H), 4.40-4.10 (m, 2H), 4.10-3.60 (m, 4H), 3.56 (s, 3H), 3.12 (m, 1H), 2.85 (m, 1H), 2.31 (m, 1H), 2.20-1.70 (m, 3H), 1.60 (m, 1H).

Example 23: (3*R*, *SS*) and (3R, S*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[2-(2-methoxybenzenesulfinyl)ethyl]-1-azoniabicyclo[2.2.2]octane; chloride

The yield was 72 mg (47%) as a white solid. ^{1}H-NMR ($CDCl_3$): 7.62 (d, 1H), 7.52 (t, 1H), 7.35-7.00 (m, 8H), 6.96 (t, 2H), 5.12 (m, 1H), 4.76 (s, 2H), 4.20 (m, 1H), 4.10-3.80 (m, 2H), 3.94 (s, 3H), 3.75-3.50 (m, 4H), 3.41 (m, 1H), 3.17 (m, 1H), 2.85 (m, 1H), 2.33 (m, 1H), 2.20-1.80 (m, 3H), 1.59 (m, 1H).

Example 24: (*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-(2-methoxyphenylsulfanylcarbonylmethyl)-1-azoniabicyclo[2.2.2]octane;

bromide

The yield was 66 mg (31%) as a yellow solid. ^{1}H-NMR ($CDCl_3$): 7.35-7.00 (m, 10H), 6.97 (t, 2H), 5.25-5.05 (m, 3H), 4.77 (dd, 2H), 4.50-3.80 (m, 5H), 3.76 (s, 3H), 3.50 (m, 1H), 2.32 (m, 1H), 2.10-1.50 (m, 4H).

Example 25: (*R*)-1-(2-Benzoyloxyethyl)-3-[(4-fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide

The yield was 52 mg (30%) as a white solid. ^{1}H-NMR ($CDCl_3$): 8.02 (d, 2H), 7.62 (t, 1H), 7.48 (t, 2H), 7.30-6.85 (m, 8H), 5.12 (m, 1H), 4.80-4.65 (m, 4H), 4.45-3.80 (m, 6H), 3.59 (m, 1H), 3.20 (m, 1H), 2.37 (m, 1H), 2.10-1.60 (m, 4H).

Example 26: (*R*)-1-(2-Benzoylaminoethyl)-3-[(4-fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; chloride

The yield was 56 mg (39%) as a brownish solid. ^{1}H-NMR ($CDCl_3$): 9.38 (s, 1H), 8.06 (d, 2H), 7.55-7.30 (m, 4H), 7.30-7.00 (m, 5H), 6.94 (t, 2H), 5.09 (m, 1H), 4.74 (s, 2H), 4.10 (m, 1H), 4.05-3.60 (m, 5H), 3.32 (m, 1H), 2.95 (m, 1H), 2.40 (m, 2H), 2.27 (m, 1H), 2.10-1.70 (m, 3H), 1.59 (m, 1H).

Example 27: (*R*)-1-[2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)ethyl]-3-[(4-fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide

The yield was 56 mg (39%) as a brownish solid. ^{1}H-NMR ($CDCl_3$): 7.82-7.70 (m, 4H), 7.35-7.00 (m, 6H), 6.96 (t, 2H), 5.13 (m, 1H), 4.77 (s, 2H), 4.35-3.80 (m, 8H), 3.40-2.95 (m, 2H), 2.35 (m, 1H), 2.10-1.70 (m, 3H), 1.59 (m, 1H).

Example 28: (*R*)-1-(2-Benzenesulfonylaminoethyl)-3-[(4-fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide

The yield was 64 mg (39%) as a brownish solid. ^{1}H-NMR ($CDCl_3$): 7.90-7.76 (m, 3H), 7.47 (dd, 2H), 7.45-7.30 (m, 1H), 7.35 (dd, 1H), 7.25-7.00 (m, 4H), 6.93 (t, 2H), 5.03 (m, 1H), 4.75 (dd, 2H), 4.00 (m, 1H), 3.80-3.50 (m, 6H), 3.40-3.00 (m, 3H), 2.37 (m, 1H), 2.10-1.60 (m, 4H).

Example 29: (*R*)-1-[3-(2-Cyanophenoxy)propyl]-3-[(4-fluorobenzyl)-(2-

fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; chloride
The yield was 92 mg (55%) as a yellow solid. ^{1}H-NMR ($CDCl_3$): 7.54 (m, 2H), 7.35-6.90 (m, 10H), 5.17 (m, 1H), 4.78 (s, 2H), 4.35-3.80 (m, 8H), 3.31 (m, 1H), 3.01 (m, 1H), 2.45-1.80 (m, 6H), 1.65 (m, 1H).

Example 30: (*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[3-(3-nitrophenoxy)propyl]-1-azoniabicyclo[2.2.2]octane; chloride
The yield was 250 mg (47%) as a white solid. ^{1}H-NMR ($CDCl_3$): 7,83 (ddd, 1H), 7.67 (t, 1H), 7.44 (t, 1H), 7.33-7.00 (m, 7H), 6.96 (t, 2H), 5.16 (m, 1H), 4.78 (s, 2H), 4.18 (t, 2H), 4.15-3.60 (m, 6H), 3.25 (m, 1H), 2.97 (m, 1H), 2.35-1.80 (m, 6H), 1.63 (m, 1H).

Example 31: (*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[3-(4-methylpyrimidin-2-yloxy)propyl]-1-azoniabicyclo[2.2.2]octane; bromide
The yield was 25 mg (11%) as a orange solid. ^{1}H-NMR ($CDCl_3$): 7.50-6.90 (m, 10H), 5.16 (m, 1H), 4.78 (s, 2H), 4.15 (m, 1H), 4.15-3.40 (m, 7H), 3.22 (m, 1H), 2.92 (m, 1H), 2.40-1.80 (m, 9H), 1.63 (m, 1H).

Example 32: (*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[3-(pyridin-2-ylsulfanyl)propyl]-1-azoniabicyclo[2.2.2]octane; bromide
The yield was 24 mg (11%) as a red oil. ^{1}H-NMR ($CDCl_3$): 8.41 (ddd, 1H), 7.51 (td, 1H), 7.35-6.90 (m, 10H), 5.13 (m, 1H), 4.76 (s, 2H), 4.20-3.55 (m, 6H), 3.23 (t, 2H), 3.15 (m, 1H), 2.85 (m, 1H), 2.34 (m, 1H), 2.20-1.60 (m, 6H).

Example 33: (*R*)-1-[3-(Benzooxazol-2-ylsulfanyl)propyl]-3-[(4-fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; chloride
The yield was 80 mg (35%) as a orange solid. ^{1}H-NMR ($CDCl_3$): 7.35-7.00 (m, 10H), 6.96 (t, 2H), 5.17 (m, 1H), 4.77 (s, 2H), 4.20 (m, 1H), 4.00-3.55 (m, 5H), 3.69 (t, 2H), 3.15 (m, 1H), 2.85 (m, 1H), 2.57 (m, 2H), 2.40-1.80 (m, 4H), 1.57 (m, 1H).

Example 34: (*R*)-1-[3-(2-Fluorobenzenesulfonyl)propyl]-3-[(4-fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; chloride

The yield was 81 mg (45%) as a brown solid. ^{1}H-NMR ($CDCl_3$): 7.89 (td, 1H), 7.68 (tdd, 1H), 7.34 (td, 1H), 7.30-7.00 (m, 7H), 6.96 (t, 2H), 5.12 (m, 1H), 4.76 (s, 2H), 4.10 (m, 1H), 4.00-3.60 (m, 5H), 3.48 (t, 2H), 3.21 (m, 1H), 2.93 (m, 1H), 2.50-1.70 (m, 6H), 1.60 (m, 1H).

Example 35: (*R*)-1-{3-[Acetyl-(3-Chlorophenyl)amino]propyl}-3-[(4-fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; chloride

The yield was 23 mg (9%) as a brown solid. ^{1}H-NMR ($CDCl_3$): 7.30-7.02 (m, 10H), 6.97 (t, 2H), 5.14 (m, 1H), 4.77 (s, 2H), 4.19 (m, 1H), 4.09-3.50 (m, 5H), 3.69 (t, 2H), 3.20 (m, 1H), 2.90 (m, 1H), 2.50-1.80 (m, 6H), 2.17 (s, 3H), 1.58 (m, 1H).

Example 36: (*R*)-1-{3-[Benzyloxycarbonyl-(2-fluorophenyl)amino]propyl}-3-[(4-fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; chloride

The yield was 410 mg (65%) as a white solid. ^{1}H-NMR ($CDCl_3$): 7.38-7.02 (m, 15H), 6.96 (t, 2H), 5.09 (s, 2H), 5.08 (m, 1H), 4.76 (dd, 2H), 4.20-3.30 (m, 6H), 3.72 (t, 2H), 3.05 (m, 1H), 2.77 (m, 1H), 2.27 (m, 1H), 2.10-1.80 (m, 5H) 1.56 (m, 1H).

Example 37: (*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-(2-phenylcarbamoylethyl)-1-azoniabicyclo[2.2.2]octane; chloride

The yield was 95 mg (66%) as a yellow solid. ^{1}H-NMR ($CDCl_3$): 10.95 (s, 1H), 7.79 (d, 2H), 7.31-7.00 (m, 9H), 6.95 (t, 2H), 5.11 (m, 1H), 4.75 (s, 2H), 4.09 (m, 1H), 3.95-3.10 (m, 6H), 2.87 (m, 1H), 2.29 (m, 1H), 2.10-1.70 (m, 5H) 1.58 (m, 1H).

Example 38: (*R*)-1-(3-Benzoyloxypropyl)-3-[(4-fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide

The yield was 22 mg (13%) as a yellow solid. ^{1}H-NMR ($CDCl_3$): 8.02 (m, 2H), 7.56 (m, 1H), 7.45 (m, 2H), 7.30-6.92 (m, 8H), 5.15 (m, 1H), 4.75 (s, 2H), 4.43 (m, 2H), 4.15 (m, 1H), 4.05-3.77 (m, 5H), 3.18 (m, 1H), 2.87 (m, 1H), 2.42-1.80 (m, 6H), 1.56 (m, 1H).

Example 39: (*R*)-1-[2-(4-acetylaminophenylsulfanyl)ethyl]-3-[(4-fluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide

The yield was 99 mg (33%) as a yellow solid. ^{1}H-NMR ($CDCl_3$): 9.66 (s, 1H), 7.62 (d, 2H), 7.26-7.14 (m, 6H), 7.00-6.90 (m, 6H), 5.05 (m, 1H), 4.80 (m, 2H), 4.10 (m, 1H), 3.90-3.40 (m, 6H), 3.10 (m, 3H), 2.30 (m, 1H), 2.17 (s, 3H), 2.10-1.50 (m, 4H).

Example 40: (*3R, 2'RS*)-3-[(3,4-Difluorobenzyl)phenylcarbamoyloxy]-1-[3-(4-fluorophenoxy)-2-hydroxypropyl]-1-azoniabicyclo[2.2.2]octane; hydroxide

The yield was 18 mg (8%), as a yellow oil. ^{1}H-NMR ($CDCl_3$): 7.45-7.80 (m, 12H), 6.38 (br, 1H), 5.12 (m, 1H), 4.90-4.58 (m, 3H), 4.35-4.15 (m, 1H), 4.10-3.44 (m, 8H), 3.10 (br, 1H), 2.35 (m, 1H), 2.10-1.60 (m, 4H).

Example 41: (*R*)-1-[2-(3-Chloro-5-fluorophenyl)ethyl]-3-[(3,4-difluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; chloride

The yield was 101 mg, as a white solid. ^{1}H-NMR ($CDCl_3$): 7.67 (m, 1H), 7.38- 6.85 (m, 9H), 5.17 (m, 1H), 4.76 (s, 2H), 4.33-3.70 (m, 7H), 3.57 (m, 1H), 3.33 (m, 1H), 3.17 (m, 2H), 2.99 (m, 1H), 2.35 (m, 1H), 2.10-1.80 (m, 3H), 1.60 (m,1H).

Example 42: (*R*)-1-(2-Cyclohexylsulfanylethyl)-3-[(3,4-difluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; chloride

The yield was 58 mg (28%) as a yellow oil. ^{1}H-NMR ($CDCl_3$): 7.30 ((m, 1H), 7.20-7.00 (m, 5H), 6.95 (m, 1H), 5.13 (m, 1H), 4.75 (s, 2H), 4.25-4.00 (m, 2H), 4.00-3.80 (m, 1H), 3.73 (m, 2H), 3.50 (m, 1H), 3.27 (m, 1H), 2.88 (m, 4H), 2.35 (m, 1H), 2.10-1.80 (m, 4H) 1.80-1.50 (m, 4H), 1.45-1.10 (m, 6H).

Example 43: (*R*)-1-(2-Benzenesulfonylethyl)-3-[(3,4-difluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; chloride

The yield was 43 mg (20%) as a yellow oil. ^{1}H-NMR ($CDCl_3$): 7.35-6.90 (m, 12H), 5.08 (m, 1H), 4.74 (s, 2H), 4.15-3.85 (m, 3H), 3.75-3.45 (m,

4H), 3.20-3.05 (m, 1H), 2.95-2.80 (m, 1H), 2.71 (t, 2H), 2.35 (m, 1H), 2.10-1.70 (m, 4H).

Example 44: (*R*)-3-[(3,4-Difluorobenzyl)-*m*-tolylcarbamoyloxy]-1-(2-phenylsulfanylethyl)-1-azoniabicyclo[2.2.2]octane; chloride

The yield was 170 mg (63%) as white solid. ^{1}H-NMR ($CDCl_3$): 7.58 (s, 2H), 7.36-6.94 (m, 10H), 5.57 (m, 2H), 5.06 (m, 1H), 4.74 (s, 2H), 4.13 (m, 1H), 4.00-3.40 (m, 6H), 3.10 (br, 1H), 2.32 (m, 1H), 2.32 (s, 3H), 2.20-1.50 (m, 4H).

Example 45: (*R*)-3-[(3,4-Difluorobenzyl)-*m*-tolylcarbamoyloxy]-1-[3-(4-fluorophenylsulfanyl)propyl]-1-azoniabicyclo[2.2.2]octane; chloride

The yield was 96 mg (43%) as a green solid. ^{1}H-NMR ($CDCl_3$): 7.40 (dd, 2H), 7.25-6.80 (m, 9H), 5.09 (m, 1H), 4.72 (m, 2H), 4.11 (m, 1H), 3.90-3.60 (m, 5H), 3.27 (m, 1H), 2.96 (t, 2H), 2.64 (m, 1H), 2.31 (m, 1H), 2.31 (s, 3H), 2.10-1.70 (m, 5H), 1.55 (m, 1H).

Example 46: (*R*)- 3-[(3,4-Difluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; bromide

The yield was 145 mg (56%) as a white solid. ^{1}H-NMR ($CDCl_3$): 7.37-7.16 (m, 3H), 7.15-6.96 (m, 6H), 6.94-6.80 (m, 3H), 5.11 (m, 1H), 4.81 (m, 2H), 4.50-4.12 (m, 6H), 4.10-3.70 (m, 3H), 3.45 (br, 1H), 2.32 (m, 1H), 2.02 (m, 2H), 1.90-1.60 (m, 2H).

Example 47: (*R*)-3-[(3,4-Difluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; bromide

The yield was 151 mg (67%) as a white. ^{1}H-NMR ($CDCl_3$): 7.37-6.82 (m, 12H), 5.09 (m, 1H), 4.78 (m, 2H), 4.07 (m, 1H), 3.68 (m, 5H), 3.25 (br, 1H), 3.00 (br, 1H), 2.70 (m, 2H), 2.32 (m, 1H), 2.20-1.60 (m, 6H).

Example 48: (*R*)-1-Cyclopropylmethyl-3-[(2-fluorophenyl)-(3,4,5-trifluorobenzyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide

The yield was 107 mg (54%) as a white solid. ^{1}H-NMR ($CDCl_3$): 7.40-7.05 (m, 4H), 6.90 (m, 1H), 6.89 (dd, 1H), 5.13 (m, 1H), 4.74 (s, 2H), 4.20-3.90 (m, 3H), 3.85-3.60 (m, 2H), 3.55 (m, 2H), 3.38 (m, 1H), 3.09 (m, 1H), 2.35

(m, 1H), 2.20-1.85 (m, 3H) 1.54 (m, 1H), 0.93 (m, 1H), 0.80 (m, 2H), 0.57 (m, 2H).

Example 49: (*R*)-1-Benzyl-3-[(2-fluorophenyl)-(3,4,5-trifluorobenzyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide
The yield was 119 mg (56%) as a white solid. ^{1}H-NMR ($CDCl_3$): 7.55 (m, 2H), 7.44 (s, 3H), 7.32-7.05 (m, 4H), 7.00- 6.89 (m, 2H), 5.08 (m, 2H), 4.91 (m, 1H), 4.69 (s, 2H), 4.07 (m, 4H), 3.77 (m, 2H), 3.32 (br, 1H), 2.95 (br, 1H), 2.31 (m, 1H), 2.20-1.45 (m, 4H).

Example 50: (*R*)-3-[(2-Fluorophenyl)-(3,4,5-trifluorobenzyl)carbamoyloxy]-1-(2-phenylsulfanylethyl)-1-azoniabicyclo[2.2.2]octane; chloride
The yield was 36 mg (17%) as a yellow solid. ^{1}H-NMR ($CDCl_3$): 7.46-7.22 (m, 6H), 7.20-7.02 (m, 3H), 6.96-6.83 (m, 2H), 5.12 (m, 1H), 4.73 (s, 2H), 4.25-3.95 (m, 3H), 3.80-3.50 (m, 3H), 3.45-3.20 (m, 3H), 2.90 (br, 1H), 2.33 (m, 1H), 2.10-1.80 (m, 3H), 1.59 (m, 1H).

Example 51: (*R*)-3-[(3-Fluorophenyl)-(3,4,5-trifluorobenzyl)carbamoyloxy]-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; bromide
The yield was 126 mg (55%) as a white solid. ^{1}H-NMR ($CDCl_3$): 7.40-7.21 (m, 3H), 7.10-6.80 (m, 9H), 5.13 (m, 1H), 4.82 (m, 2H), 4.16 (m, 1H), 4.06 (t, 2H), 4.00-3.60 (m, 6H), 3.30 (br, 1H), 2.38 (m, 1H), 2.25 (m, 2H), 2.15-1.60 (m, 4H).

Example 52: (*R*)-1-[3-(3,4-Difluorophenoxy)propyl]-3-[(3-fluorophenyl)-(3,4,5-trifluorobenzyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; chloride
^{1}H-NMR ($CDCl_3$): 7.33 (m, 1H), 7.12-6.85 (m, 6H), 6.69 (ddd, 1H), 6.57 (m, 1H), 5.16 (m, 1H), 4.83 (m, 2H), 4.18 (m, 1H), 4.04 (t, 2H), 4.00-3.60 (m, 6H), 3.30 (br, 1H), 2.38 (m, 1H), 2.34 (m, 2H), 2.15-1.60 (m, 4H).

Example 53: (*R*)-1-(2-Oxo-2-phenylethyl)-3-(thiophen-2-ylmethyl-*m*-tolylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; bromide
The yield was 23 mg (15%) as a white solid. ^{1}H-NMR ($CDCl_3$): 8.09 (d, 2H), 7.56 (t, 1H), 7.42 (t, 2H), 7.23 (dd, 1H), 7.21 (s, 1H), 7.13-6.96 (m, 3H), 6.93-6.83 (m, 2H), 5.79 (s, 2H), 5.15 (m, 1H), 4.95 (m, 2H), 4.60-3.80

(m, 4H), 3.61 (m, 1H), 3.29 (m, 1H), 2.33 (m, 1H), 2.32 (s, 3H), 2.20-1.50 (m, 4H).

Example 54: (*R*)-1-(3-Phenylpropyl)-3-(thiophen-2-ylmethyl-*m*-tolylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; bromide

The yield was 36 mg (23%) as a white solid. ^{1}H-NMR ($CDCl_3$): 7.34-7.18 (m, 5H), 7.08 (d, 1H), 7.01 (d, 1H), 6.94-6.82 (m, 5H), 5.11 (m, 1H), 4.92 (s, 2H), 4.45-3.90 (m, 6H), 3.85-3.60 (m, 2H), 3.15 (m, 1H), 3.01 (m, 1H), 2.41 (m, 1H), 2.31 (s, 3H), 2.20-1.61 (m, 4H).

Example 55: (*R*)-1-Benzyl-3-[(2-fluorophenyl)thiophen-2-ylmethylcarbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide

The yield was 163 mg (75%) as a yellow solid. ^{1}H-NMR ($CDCl_3$): 7.75-7.35 (m, 5H), 7.25-6.82 (m, 7H), 5.12 (m, 1H), 5.20-4.80 (m, 5H), 4.40-3.40 (m,4H), 3.19 (m, 1H), 3.01 (t, 2H), 2.79 (m, 1H), 2.27 (m, 1H), 2.20-1.50 (m, 4H).

Example 56: (*R*)-1-Cyclobutylmethyl-3-[(3-fluorophenyl)thiophen-2-ylmethylcarbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide

The yield was 153 mg (72%) as an oil. ^{1}H-NMR ($CDCl_3$): 7.33 (td, 1H), 7.25 (dd, 1H), 7.05-6.88 (m, 5H), 5.15 (m, 1H), 5.00 (m, 2H), 4.15-4.00 (m, 1H), 3.80-3.95 (m, 2H), 3.70-3.50 (m, 1H), 3.60 (dd, 2H), 3.30 (m, 1H), 2.73 (m, 1H), 2.42 (m, 1H), 2.20-0.90 (m, 11H).

Example 57: (*R*)-3-[(3-Methylthiophen-2-ylmethyl)phenylcarbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; bromide

The yield was 170 mg (56%) as an oil. ^{1}H-NMR ($CDCl_3$): 7.35-7.25 (m, 1H), 7.32 (t, 2H), 7.10-6.80 (m, 6H), 6.58 (m, 1H), 6.51 (m, 1H), 5.13 (m, 1H), 4.87 (m, 2H), 4.55-4.30 (m, 3H), 4.30-4.00 (m, 4H), 3.80 (m, 2H), 3.15 (br, 1H), 2.42 (m, 1H), 2.41 (s, 3H), 2.20-1.50 (m, 4H).

Example 58: (*R*)-3-[(4-Bromothiophen-2-ylmethyl)phenylcarbamoyloxy]-1-Cyclopropylmethyl-1-azoniabicyclo[2.2.2]octane; bromide

The yield was 90 mg (60%) as a white solid. ^{1}H-NMR ($CDCl_3$): 7.43-7.28 (m, 3H), 7.28-7.10 (m, 2H), 7.15 (d, 1H), 6.83 (s, 1H), 5.12 (m, 1H), 4.91

(m, 2H), 4.17 (ddd, 1H), 4.05-3.30 (m, 4H), 3.57 (d, 2H), 2.93 (br, 1H), 2.35 (m, 1H), 2.20-1.50 (m, 4H), 0.97 (br, 1H), 0.78 (m, 2H), 0.56 (m, 2H).

Example 59: (*R*)-3-[(4-Bromothiophen-2-ylmethyl)phenylcarbamoyloxy]-1-phenylsulfanylmethyl-1-azoniabicyclo[2.2.2]octane; chloride

The yield was 89 mg (57%) as a white solid. ^{1}H-NMR ($CDCl_3$): 7.68 (m, 1H), 7.58 (br, 3H), 7.45-7.30 (m, 6H), 7.13 (m, 2H), 6.81 (s, 1H), 5.54 (m, 2H), 5.07 (m, 1H), 4.90 (m, 2H), 4.12 (m, 1H), 3.90-3.60 (m, 3H), 3.45 (m, 1H), 3.11 (m, 1H), 2.33 (m, 1H), 2.20-1.50 (m, 4H).

Example 60: (*R*)-1-[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]-3-[(5-methylthiophen-2-ylmethyl)phenylcarbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide

The yield was 310 mg (63%) as a white solid. ^{1}H-NMR ($CDCl_3$): 7.36-7.05 (m, 5H), 7.29 (d, 1H), 7.15 (s, 1H), 6.93 (d, 1H), 6.61 (d, 1H), 6.54 (d, 1H), 5.08 (m, 1H), 4.83 (m, 2H), 4.47 (t, 2H), 4.13 (ddd, 1H), 4.09-3.80 (m, 2H), 3.80-3.50 (m, 3H), 3.20 (br, 1H), 3.09 (t, 2H), 2.89 (t, 2H), 2.85 (br, 1H), 2.39 (s, 3H), 2.29 (m, 1H), 2.21-1.80 (m, 4H), 1.52 (br, 1H).

Example 61: (*R*)-3-[(5-Chlorothiophen-2-ylmethyl)-(2-fluorophenyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; bromide

The yield was 200 mg (98%) as a yellow solid. ^{1}H-NMR ($CDCl_3$): 7.40-7.20 (m, 4H), 7.15-6.95 (m, 3H), 6.95-6.80 (m, 2H), 6.69 (br, 1H), 6.61 (br, 1H), 5.13 (m, 1H), 4.80 (s, 2H), 4.60-4.00 (m, 8H), 3.53 (m, 1H), 3.06 (m, 1H), 2.40 (m, 1H), 2.20-1.50 (m, 4H).

Example 62: (*R*)-3-[(5-Bromothiophen-2-ylmethyl)phenylcarbamoyloxy]-1-Cyclopropylmethyl-1-azoniabicyclo[2.2.2]octane; bromide

The yield was 100 mg (60%) as a white solid. ^{1}H-NMR ($CDCl_3$): 7.45-7.25 (m, 3H), 7.25-7.09 (m, 2H), 6.87 (d, 1H), 6.64 (br, 1H), 5.12 (m, 1H), 4.89 (m, 2H), 4.40 (m, 1H), 4.17 (m, 1H), 4.05-3.80 (m, 2H), 3.80-3.05 (m, 6H), 2.36 (m, 1H), 2.20-1.50 (m, 4H), 0.95 (m, 1H), 0.81 (m, 2H), 0.58 (m, 2H).

Example 63: (*R*)-3-[(5-Bromothiophen-2-ylmethyl)phenylcarbamoyloxy]-1-

(2-phenylsulfanylethyl)-1-azoniabicyclo[2.2.2]octane; chloride
The yield was 50 mg (28%) as a white solid. ^{1}H-NMR ($CDCl_3$): 7.47-7.20 (m, 8H), 7.13 (br, 2H), 6.85 (d, 1H), 6.62 (d, 1H), 5.11 (m, 1H), 4.84 (s, 2H), 4.15 (m, 1H), 4.00 (m, 2H), 3.85-3.50 (m, 4H), 3.45-3.20 (m, 2H), 2.95 (br, 1H), 2.33 (m, 1H), 2.20-1.80 (m, 3H), 1.62 (m, 1H).

Example 64: (*R*)-3-[(5-Bromothiophen-2-ylmethyl)-*m*-tolylcarbamoyloxy]-1-phenylsulfanylmethyl-1-azoniabicyclo[2.2.2]octane; chloride
The yield was 83 mg (79%) as a yellow solid. ^{1}H-NMR ($CDCl_3$): 7.58 (m, 2H), 7.46-7.31 (m, 3H), 7.21 (d, 1H), 7.12 (m, 1H), 7.02-6.86 (m, 2H), 6.86 (d, 1H), 6.64 (m, 1H), 5.55 (m, 2H), 5.07 (m, 1H), 4.83 (s, 2H), 4.15-3.60 (m, 4H), 3.40 (br, 1H), 3.05 (br, 1H), 2.34 (s, 3H), 2.33 (m, 1H), 2.20-1.50 (m, 4H).

Example 65: (*R*)-3-[(5-Bromothiophen-2-ylmethyl)-(4-fluorophenyl)carbamoyloxy]-1-cyclopropylmethyl-1-azoniabicyclo[2.2.2]octane; bromide
The yield was 81 mg (62%) as a brownish solid. ^{1}H-NMR ($CDCl_3$): 7.32-7.12 (m, 2H), 7.04 (t, 2H), 6.87 (d, 1H), 6.63 (m, 1H), 5.11 (m, 1H), 5.05-4.60 (m, 2H), 4.15 (m, 1H), 4.00-3.70 (m, 3H), 3.65-3.45 (m, 3H), 3.15 (br, 1H), 2.37 (m, 1H), 2.15-1.55 (m, 4H), 0.98 (m, 1H), 0.80 (m, 2H), 0.59 (m, 2H).

Example 66: (*R*)-3-[(5-Bromothiophen-2-ylmethyl)-(4-fluorophenyl)carbamoyloxy]-1-(2-oxo-2-phenylethyl)-1-azoniabicyclo[2.2.2]octane; bromide
The yield was 110 mg (76%) as a yellow solid. ^{1}H-NMR ($CDCl_3$): 8.12 (d, 2H), 7.58 (t, 1H), 7.42 (t, 2H), 7.36-7.24 (m, 2H), 7.03 (t, 2H), 6.86 (d, 1H), 6.63 (m, 1H), 5.85 (s, 2H), 5.18 (m, 1H), 5.00 (m, 1H), 4.75-3.90 (m, 6H), 3.66 (m, 1H), 2.35 (m, 1H), 2.15-1.55 (m, 4H).

Example 67: (*R*)-3-[(5-Bromothiophen-2-ylmethyl)(4-fluorophenyl)carbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; bromide

The yield was 107 mg (73%) as a yellow solid. ^{1}H-NMR ($CDCl_3$): 7.33-7.15 (m, 7H), 7.02 (t, 2H), 6.84 (d, 1H), 6.61 (m, 1H), 5.09 (m, 1H), 5.02-4.60 (m, 2H), 4.12 (m, 1H), 3.80-3.55 (m, 5H), 3.45 (br, 1H), 3.10 (br, 1H), 2.70 (t, 2H), 2.50-1.75 (m, 7H), 1.60 (m, 1H).

Example 68: (*R*)-1-Cyclobutylmethyl-3-[(3-fluorophenyl)thiophen-3-ylmethylcarbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide

The yield was 89 mg (42%) as white solid. ^{1}H-NMR ($CDCl_3$): 7.40-7.30 (m, 3H), 7.16 (s, 1H), 7.03-6.87 (m, 3H), 5.11 (m, 1H), 4.86 (m, 2H), 4.08 (m, 1H), 3.90-3.70 (m, 2H), 3.70-3.50 (m, 1H), 3.59 (d, 2H), 3.35 (m, 1H), 3.02 (m, 1H), 2.72 (m, 1H), 2.36 (m, 1H), 2.20-0.90 (m, 11H).

Example 69: (*R*)-3-[(3-Fluorophenyl)thiophen-3-ylmethylcarbamoyloxy]-1-(2-oxo-2-phenylethyl)-1-azoniabicyclo[2.2.2]octane; bromide

The yield was 161 mg (68%) as a white solid. ^{1}H-NMR ($CDCl_3$): 8.10 (d, 2H), 7.56 (t, 1H), 7.43 (t, 2H), 7.32-7.18 (m, 3H), 7.14 (m, 1H), 7.05-6.85 (m, 3H), 5.86 (s, 2H), 5.16 (m, 1H), 4.77 (m, 2H), 4.60-3.90 (m, 5H), 3.70 (m, 1H), 2.34 (m, 1H), 2.20-1.50 (m, 4H).

Example 70: (*R*)-3-Cyclohexylmethylphenylcarbamoyloxy-1-(2-oxo-2-phenylethyl)-1-azoniabicyclo[2.2.2]octane; bromide

The yield was 120 mg (75%) as an oil. ^{1}H-NMR ($CDCl_3$): 8.10 (d, 2H), 7.58 (t, 1H), 7.43 (t, 2H), 7.40-7.20 (m, 5H), 5.75 (s, 2H), 5.09 (m, 1H), 4.51-3.90 (m, 5H), 3.55 (d, 2H), 2.95 (br, 1H), 2.35 (m, 1H), 2.15-0.90 (m, 15H).

Example 71: (*R*)-3-Cyclohexylmethylphenylcarbamoyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; bromide

The yield was 40 mg (35%) as an oil. ^{1}H-NMR ($CDCl_3$): 7.34 (t, 2H), 7.30-7.15 (m, 4H), 7.05 (t, 2H), 6.88 (d, 2H), 5.07 (m, 1H), 4.55-3.90 (m, 6H), 3.87-3.60 (m, 3H), 3.48 (d, 2H), 2.95 (br, 1H), 2.35 (m, 1H), 2.15-0.90 (m, 15H).

The following compounds were also prepared, and they have been identified by ^{1}H-NMR:

(*R*)-3-(Benzylphenylcarbamoyloxy)-1-Cyclopropylmethyl-1-azoniabicyclo[2.2.2]octane, bromide

(*R*)-3-(Benzylphenylcarbamoyloxy)-1-Cyanomethyl-1-azoniabicyclo[2.2.2]octane; bromide

(*R*)-1-Benzyl-3-(benzylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; bromide

(*R*)-3-(Benzylphenylcarbamoyloxy)-1-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]-1-azoniabicyclo[2.2.2]octane; bromide

(*R*)-3-(Benzylphenylcarbamoyloxy)-1-(4-methoxybenzyl)-1-azoniabicyclo[2.2.2]octane; chloride

(*R*)-3-(Benzylphenylcarbamoyloxy)-1-(2-oxo-2-phenylethyl)-1-azoniabicyclo[2.2.2]octane; bromide

(*R*)-3-(Benzylphenylcarbamoyloxy)-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; bromide

(*R*)- 3-(Benzylphenylcarbamoyloxy)-1-[2-(4-fluorophenoxy)ethyl]-1-azoniabicyclo[2.2.2]octane; chloride

(*R*)-3-(Benzylphenylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; bromide

(*R*)-3-(Benzylphenylcarbamoyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; chloride

(*R*)- 3-(Benzylphenylcarbamoyloxy)-1-[3-(4-fluorophenoxy)-2-hydroxypropyl]-1-azoniabicyclo[2.2.2]octane; hydroxide

(*R*)-1-Cyclobutylmethyl-3-[(4-fluorobenzyl)phenylcarbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide

(*R*)-1-Benzyl-3-[(4-fluorobenzyl)phenylcarbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide

(*R*)-3-[(4-Fluorobenzyl)phenylcarbamoyloxy]-1-phenylsulfanylmethyl-1-azoniabicyclo[2.2.2]octane; chloride

(*R*)-3-[(4-Fluorobenzyl)phenylcarbamoyloxy]-1-phenethyl-1-azoniabicyclo[2.2.2]octane; bromide

(*R*)-3-[(4-Fluorobenzyl)phenylcarbamoyloxy]-1-(2-*o*-tolylethyl)-1-azoniabicyclo[2.2.2]octane; bromide

(*R*)-3-[(4-Fluorobenzyl)phenylcarbamoyloxy]-1-[2-(2-methoxyphenyl)ethyl]-1-azoniabicyclo[2.2.2]octane; bromide

(*R*)-3-[(4-Fluorobenzyl)phenylcarbamoyloxy]-1-[2-(3-methoxyphenyl)ethyl]-

1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(4-Fluorobenzyl)phenylcarbamoyloxy]-1-[2-(3-fluorophenyl)ethyl]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(4-Fluorobenzyl)phenylcarbamoyloxy]-1-(2-*p*-tolylethyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)- 3-[(4-Fluorobenzyl)phenylcarbamoyloxy]-1-[2-(4-fluorophenyl)ethyl]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-1-[2-(2,5-Dimethoxyphenyl)ethyl]-3-[(4-fluorobenzyl)phenylcarbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-1-[2-(3,4-Dimethoxyphenyl)ethyl]-3-[(4-fluorobenzyl)phenylcarbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide.
(*R*)-3-[(4-Fluorobenzyl)phenylcarbamoyloxy]-1-(2-oxo-2-phenylethyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(4-Fluorobenzyl)phenylcarbamoyloxy]-1-[2-(4-fluorophenoxy)ethyl]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(4-Fluorobenzyl)phenylcarbamoyloxy]-1-[2-(2-fluorophenylsulfanyl)ethyl]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(4-Fluorobenzyl)-*m*-tolylcarbamoyloxy]-1-phenethyl-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-1-[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]-3-[(4-fluorobenzyl)-*m*-tolylcarbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(4-Fluorobenzyl)-*m*-tolylcarbamoyloxy]-1-(2-oxo-2-phenylethyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(4-Fluorobenzyl)-*m*-tolylcarbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(4-Fluorobenzyl)-*m*-tolylcarbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(4-Fluorobenzyl)-*m*-tolylcarbamoyloxy]-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-phenylsulfanylmethyl-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-(2-*o*-tolylethyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[2-(2-methoxyphenyl)ethyl]-1-azoniabicyclo[2.2.2]octane; bromide

(*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-(2-*m*-tolylethyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[2-(3-methoxyphenyl)ethyl]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[2-(3-fluorophenyl)ethyl]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-(2-*p*-tolylethyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[2-(4-methoxyphenyl)ethyl]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-1-[2-(4-Ethoxyphenyl)ethyl]-3-[(4-fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[2-(4-fluorophenyl)ethyl]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-1-[2-(2,5-Dimethoxyphenyl)ethyl]-3-[(4-fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-phenylcarbamoylmethyl-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-(*o*-tolylcarbamoylmethyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[2-(2-fluorophenoxy)ethyl]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[2-(3-methoxyphenoxy)ethyl]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[2-(4-fluorophenoxy)ethyl]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-(2-phenylsulfanylethyl)-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[2-(2-metoxyphenylsulfanyl)ethyl]-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[2-(2-fluorophenylsulfanyl)ethyl]-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-1-[2-(2-Chlorophenylsulfanyl)ethyl]-3-[(4-fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-1-[2-(3-Chlorophenylsulfanyl)ethyl]-3-[(4-fluorobenzyl)-(2-

fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[2-(4-fluorophenylsulfanyl)ethyl]-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-1-[2-(4-Bromophenylsulfanyl)ethyl]-3-[(4-fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-1-[2-(2,4-Difluorophenylsulfanyl)ethyl]-3-[(4-fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-1-[2-(2,5-Dichlorophenylsulfanyl)ethyl]-3-[(4-fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide
(3*R*, *SS*) and (3R, S*R*)-1-(2-Benzenesulfinylethyl)-3-[(4-fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[3-(2-fluorophenoxy)propyl]-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-(3-*m*-tolyloxypropyl)-1-azoniabicyclo[2.2.2]octane; chloride .
(*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[3-(3-methoxyphenoxy)propyl]-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-1-[3-(2,4-Difluorophenoxy)propyl]-3-[(4-fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[3-(pyridin-3-yloxy)propyl]-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[3-(pyrimidin-2-yloxy)propyl]-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-(3-phenylsulfanylpropyl)-1-azoniabicyclo[2.2.2]octane.
(*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[3-(2-fluorophenylsulfanyl)propyl]-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-1-[3-(2-Chlorophenylsulfanyl)propyl]-3-[(4-fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-1-[3-(3-Chlorophenylsulfanyl)propyl]-3-[(4-fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[3-(pyridin-4-ylsulfanyl)propyl]-1-azoniabicyclo[2.2.2]octane

(*R*)-3-[(4-Fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[3-(pyrimidin-2-ylsulfanyl)propyl]-1-azoniabicyclo[2.2.2]octane

(*R*)-1-(3-Benzenesulfonylpropyl)-3-[(4-fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; chloride

(*R*)-1-[3-(3-Chlorobenzenesulfonyl)propyl]-3-[(4-fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; chloride

(*R*)-1-{3-[Acetyl-(2-fluorophenyl)amino]propyl}-3-[(4-fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; chloride

(*R*)-1-{3-[Acetyl-(3-methoxyphenyl)amino]propyl}-3-[(4-fluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; chloride

(*R*)-1-Benzyl-3-[(4-fluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide

(*R*)-3-[(4-Fluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-phenylsulfanylmethyl-1-azoniabicyclo[2.2.2]octane; chloride

(*R*)-1-[2-(2-Chlorophenyl)ethyl]-3-[(4-fluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide

(*R*)-3-[(4-Fluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-[2-(3-fluorophenyl)ethyl]-1-azoniabicyclo[2.2.2]octane; bromide

(*R*)-3-[(4-Fluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-[2-(4-methoxyphenyl)ethyl]-1-azoniabicyclo[2.2.2]octane; chloride

(*R*)-3-[(4-Fluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-[2-(4-methoxyphenyl)ethyl]-1-azoniabicyclo[2.2.2]octane; bromide

(*R*)-3-[(4-Fluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-[2-(4-fluorophenyl)ethyl]-1-azoniabicyclo[2.2.2]octane; bromide

(*R*)-1-[2-(2-Chloro-6-fluorophenyl)ethyl]-3-[(4-fluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide

(*R*)-3-[(4-Fluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; bromide

(*R*)-3-[(4-Fluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; bromide

(*R*)-1-[3-(3,4-Difluorophenoxy)propyl]-3-[(4-fluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; chloride

(*R*)-1-[3-(3-Chlorophenylsulfanyl)propyl]-3-[(4-fluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; chloride

(*R*)-3-[(4-Fluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-[3-(4-

fluorophenylsulfanyl)propyl]-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-3-[(3,4-Difluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-phenethyl-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(3,4-Difluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[2-(4-methoxyphenyl)ethyl]-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-3-[(3,4-Difluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-(2-oxo-2-phenylethyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(3,4-Difluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(3,4-Difluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[2-(4-fluorophenoxy)ethyl]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(3,4-Difluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-(2-phenylsulfanylethyl)-1-azoniabicyclo[2.2.2]octane; chloride
(*3R,2'RS*)-3-[(3,4-Difluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[3-(4-fluorophenoxy)-2-hydroxypropyl]-1-azoniabicyclo[2.2.2]octane; hydroxide
(*R*)-3-[(3,4-Difluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(3,4-Difluorobenzyl)-(2-fluorophenyl)carbamoyloxy]-1-[3-(2,4-difluorophenoxy)propyl]-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-3-[(3,4-Difluorobenzyl)-*m*-tolylcarbamoyloxy]-1-phenethyl-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(3,4-Difluorobenzyl)-*m*-tolylcarbamoyloxy]-1-[2-(2-fluorophenyl)ethyl]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(3,4-Difluorobenzyl)-*m*-tolylcarbamoyloxy]-1-[2-(4-methoxyphenyl)ethyl]-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-3-[(3,4-Difluorobenzyl)-*m*-tolylcarbamoyloxy]-1-(2-oxo-2-phenylethyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(3,4-Difluorobenzyl)-*m*-tolylcarbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(3,4-Difluorobenzyl)-*m*-tolylcarbamoyloxy]-1-[2-(4-fluorophenoxy)ethyl]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(3,4-Difluorobenzyl)-*m*-tolylcarbamoyloxy]-1-(2-phenylsulfanylethyl)-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-3-[(3,4-Difluorobenzyl)-m-tolylcarbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; bromide

(*R*)-3-[(3,4-Difluorobenzyl)-*m*-tolylcarbamoyloxy]-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-3-[(3,4-Difluorobenzyl)-*m*-tolylcarbamoyloxy]-1-(3-phenylsulfanylpropyl)-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-3-[(3,4-Difluorobenzyl)-*m*-tolylcarbamoyloxy]-1-[3-(2-fluorophenylsulfanyl)propyl]-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-1-[3-(3-Chlorophenylsulfanyl)propyl]-3-[(3,4-difluorobenzyl)-*m*-tolylcarbamoyloxy]-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-1-Cyclopropylmethyl-3-[(3,4-difluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(3,4-Difluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-phenethyl-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(3,4-Difluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-[2-(4-methoxyphenyl)ethyl]-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-3-[(3,4-Difluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-[2-(4-methoxyphenyl)ethyl]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(3,4-Difluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-[2-(4-fluorophenoxy)ethyl]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(3,4-Difluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-(2-phenylsulfanylethyl)-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-3-[(3,4-Difluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(3,4-Difluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-[3-(4-fluorophenoxy)propyl]-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-3-[(2-Fluorophenyl)-(3,4,5-trifluorobenzyl)carbamoyloxy]-1-phenethyl-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(2-Fluorophenyl)-(3,4,5-trifluorobenzyl)carbamoyloxy]-1-[2-(4-methoxyphenyl)ethyl]-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-3-[(2-Fluorophenyl)-(3,4,5-trifluorobenzyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-1-[2-(4-Fluorophenoxy)ethyl]-3-[(2-fluorophenyl)-(3,4,5-trifluorobenzyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(2-Fluorophenyl)-(3,4,5-trifluorobenzyl)carbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(3-Fluorophenyl)-(3,4,5-trifluorobenzyl)carbamoyloxy]-1-phenethyl-

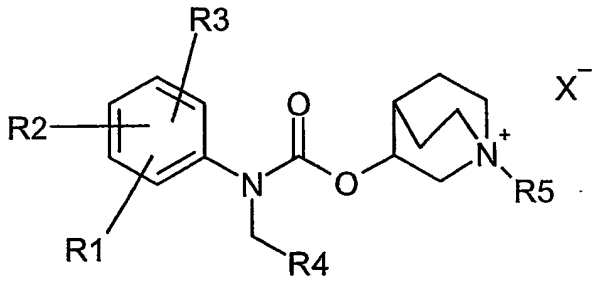
1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-1-[2-(2-Fluorophenyl)ethyl]-3-[(3-fluorophenyl)-(3,4,5-trifluorobenzyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(3-Fluorophenyl)-(3,4,5-trifluorobenzyl)carbamoyloxy]-1-[2-(4-methoxyphenyl)ethyl]-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-1-[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]-3-[(3-fluorophenyl)-(3,4,5-trifluorobenzyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(3-Fluorophenyl)-(3,4,5-trifluorobenzyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-1-[2-(4-Fluorophenoxy)ethyl]-3-[(3-fluorophenyl)-(3,4,5-trifluorobenzyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(3-Fluorophenyl)-(3,4,5-trifluorobenzyl)carbamoyloxy]-1-(2-phenylsulfanylethyl)-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-3-[(3-Fluorophenyl)-(3,4,5-trifluorobenzyl)carbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-1-Cyclobutylmethyl-3-(thiophen-2-ylmethyl-*m*-tolylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-1-Phenethyl-3-(thiophen-2-ylmethyl-*m*-tolylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-1-[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]-3-(thiophen-2-ylmethyl-*m*-tolylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)- 1-(2-Thiophen-2-ylethyl)-3-(thiophen-2-ylmethyl-*m*-tolylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-1-(3-Phenoxypropyl)-3-(thiophen-2-ylmethyl-*m*-tolylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-1-Cyclopropylmethyl-3-[(2-fluorophenyl)thiophen-2-ylmethylcarbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(2-Fluorophenyl)thiophen-2-ylmethylcarbamoyloxy]-1-phenethyl-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(2-Fluorophenyl)thiophen-2-ylmethylcarbamoyloxy]-1-[2-(4-methoxyphenyl)ethyl]-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-3-[(2-Fluorophenyl)thiophen-2-ylmethylcarbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(2-Fluorophenyl)thiophen-2-ylmethylcarbamoyloxy]-1-(2-phenylsulfanylethyl)-1-azoniabicyclo[2.2.2]octane; chloride

(*R*)-3-[(2-Fluorophenyl)thiophen-2-ylmethylcarbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(2-Fluorophenyl)thiophen-2-ylmethylcarbamoyloxy]-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-1-Benzyl-3-[(3-fluorophenyl)thiophen-2-ylmethylcarbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(3-Fluorophenyl)thiophen-2-ylmethylcarbamoyloxy]-1-phenylsulfanylmethyl-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-3-[(3-Fluorophenyl)thiophen-2-ylmethylcarbamoyloxy]-1-[2-(4-methoxyphenyl)ethyl]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-[1-[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]-3-[(3-fluorophenyl)thiophen-2-ylmethylcarbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(3-Fluorophenyl)thiophen-2-ylmethylcarbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(3-Fluorophenyl)thiophen-2-ylmethylcarbamoyloxy]-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(4-Bromothiophen-2-ylmethyl)phenylcarbamoyloxy]-1-phenethyl-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(4-Bromothiophen-2-ylmethyl)phenylcarbamoyloxy]-1-(2-oxo-2-phenylethyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(4-Bromothiophen-2-ylmethyl)phenylcarbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(4-Bromothiophen-2-ylmethyl)phenylcarbamoyloxy]-1-(2-phenylsulfanylethyl)-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-3-[(4-Bromothiophen-2-ylmethyl)phenylcarbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(4-Bromothiophen-2-ylmethyl)phenylcarbamoyloxy]-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(5-Methylthiophen-2-ylmethyl)phenylcarbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(5-Bromothiophen-2-ylmethyl)phenylcarbamoyloxy]-1-phenylsulfanylmethyl-1-azoniabicyclo[2.2.2]octane; chloride
(*R*)-3-[(5-Bromothiophen-2-ylmethyl)phenylcarbamoyloxy]-1-phenethyl-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(5-Bromothiophen-2-ylmethyl)phenylcarbamoyloxy]-1-(2-oxo-2-

phenylethyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(5-Bromothiophen-2-ylmethyl)phenylcarbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(5-Bromothiophen-2-ylmethyl)phenylcarbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(5-Bromothiophen-2-ylmethyl)phenylcarbamoyloxy]-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(5-Bromothiophen-2-ylmethyl)-*m*-tolylcarbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(5-Bromothiophen-2-ylmethyl)-*m*-tolylcarbamoyloxy]-1-(2-phenylsulfanylethyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(5-Bromothiophen-2-ylmethyl)-*m*-tolylcarbamoyloxy]-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(3-Fluorophenyl)thiophen-3-ylmethylcarbamoyloxy]-1-phenethyl-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-1-[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]-3-[(3-fluorophenyl)thiophen-3-ylmethylcarbamoyloxy]-1-azoniabicyclo[2.2.2]octane; bromide
(*R*)-3-[(3-Fluorophenyl)thiophen-3-ylmethylcarbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane
(*R*)-3-[(3-Fluorophenyl)thiophen-3-ylmethylcarbamoyloxy]-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; bromide

CLAIMS

1. A compound of general formula (I)



(I)

and prodrugs, individual isomers, racemic or non-racemic mixtures of isomers, pharmaceutically acceptable salts, polymorphs and solvates thereof,

wherein R1, R2 and R3 are radicals independently selected from the group consisting of H, OH, NO_2, SH, CN, F, Cl, Br, I, COOH, $CONH_2$, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylsulfanyl, (C_1-C_4)-alkylsulfinyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkoxyl optionally substituted with one or several F, and (C_1-C_4)-alkyl optionally substituted with one or several F or OH; alternatively, either R1 and R2, or R2 and R3 may be forming a biradical selected from the group consisting of -CH_2-CH_2-CH_2-, and -CH_2-CH_2-CH_2-CH_2-;

R4 is a radical selected from the group consisting of:

a) cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, norbornenyl, bicyclo[2.2.1]heptanyl, and 1-, 2-naphtyl, all of them optionally substituted with one or several substituents independently selected from the group consisting of OH, oxo (=O), SH, NO_2, CN, F, Cl, Br, I, $CONH_2$, COOH, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylsulfanyl, (C_1-C_4)-alkylsulfinyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkyl

optionally substituted with one or several F or OH, and (C_1-C_4)-alkoxyl optionally substituted with one or several F;

b) a *C*-linked radical of a five or six membered heterocyclic ring containing at least one heteroatom selected from the group consisting of O, S, and N, being this heterocyclic ring optionally substituted with one or several substituents independently selected from the group consisting of OH, oxo (=O), SH, NO_2, CN, F, Cl, Br, I, $CONH_2$, COOH, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylsulfanyl, (C_1-C_4)-alkylsulfinyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkyl optionally substituted with one or several F or OH, and (C_1-C_4)-alkoxyl optionally substituted with one or several F;

c) a *C*-linked radical of a bicyclic ring system consisting of a phenyl ring fused to a five or six membered heterocyclic ring containing at least one heteroatom selected from the group consisting of O, S and N, being this bicyclic ring system optionally substituted with one or several substituents independently selected from the group consisting of OH, oxo (=O), SH, NO_2, CN, F, Cl, Br, I, $CONH_2$, COOH, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylsulfanyl, (C_1-C_4)-alkylsulfinyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkyl optionally substituted with one or several F or OH, and (C_1-C_4)-alkoxyl optionally substituted with one or several F; and

d) phenyl optionally substituted with one or several substituents independently selected from the group consisting of OH, SH, NO_2, CN, F, Cl, Br, I, $CONH_2$, COOH, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylsulfanyl, (C_1-C_4)-alkylsulfinyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkyl optionally substituted with one or several F or OH, and (C_1-C_4)-alkoxyl optionally substituted with one or several F;

R5 is a radical selected from the group consisting of:

a) cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, all of them optionally substituted with one or several substituents independently selected from the group consisting of OH, oxo (=O), SH, NO_2, CN, F, Cl, Br, I, $CONH_2$, NR7CO-(C_1-C_4)-alkyl, COOH, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylsulfanyl,

(C_1-C_4)-alkylsulfinyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkyl optionally substituted with one or several F or OH, and (C_1-C_4)-alkoxyl optionally substituted with one or several F;

b) (C_5-C_{10})-alkyl;

c) (C_1-C_{10})-alkyl substituted with one or several radicals independently selected from the group consisting of R6, COR6, NH_2, NR6R7, CONR6R7, NR7COR6, OH, OR6, COOR6, OCOR6, SO_2R6, SH, SR6, SOR6, COSR6, SCOR6, CN, F, Cl, Br, NO_2, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, norbornenyl, and bicyclo[2.2.1]heptanyl;

R6 is a radical selected from the group consisting of:

a) (C_1-C_5)-alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, norbornenyl, bicyclo[2.2.1]heptanyl, all of them optionally substituted with one or several substituents independently selected from the group consisting of OH, oxo (=O), SH, NO_2, CN, F, Cl, Br, I, $CONH_2$, NR7CO-(C_1-C_4)-alkyl, COOH, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylsulfanyl, (C_1-C_4)-alkylsulfinyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkyl optionally substituted with one or several F or OH, and (C_1-C_4)-alkoxyl optionally substituted with one or several F;

b) phenyl optionally substituted with one or several substituents independently selected from the group consisting of OH, SH, NO_2, CN, F, Cl, Br, I, $CONH_2$, NR7CO-(C_1-C_4)-alkyl, COOH, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylsulfanyl, (C_1-C_4)-alkylsulfinyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkyl optionally substituted with one or several F or OH, and (C_1-C_4)-alkoxyl optionally substituted with one or several F;

c) a *C*-linked radical of a five or six membered heterocyclic ring containing at least one heteroatom selected from the group consisting of O, S, and N, being this heterocyclic ring optionally substituted with one or several substituents independently selected from the group consisting of OH, oxo (=O), SH, NO_2, CN, F, Cl, Br, I, $CONH_2$, NR7CO-(C_1-C_4)-alkyl, COOH, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylsulfanyl,

(C_1-C_4)-alkylsulfinyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkyl optionally substituted with one or several F or OH, and (C_1-C_4)-alkoxyl optionally substituted with one or several F; and

d) a *C*-linked radical of a bicyclic ring system consisting of a phenyl ring fused to a five or six membered heterocyclic ring containing at least one heteroatom selected from the group consisting of O, S and N, being this bicyclic ring system optionally substituted with one or several substituents independently selected from the group consisting of OH, oxo (=O), SH, NO_2, CN, F, Cl, Br, I, $CONH_2$, COOH, NR7CO-(C_1-C_4)-alkyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylsulfanyl, (C_1-C_4)-alkylsulfinyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkyl optionally substituted with one or several F or OH, and (C_1-C_4)-alkoxyl optionally substituted with one or several F;

R7 is a radical selected from the group consisting of H, phenoxycarbonyl, benzyloxycarbonyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylcarbonyl, (C_1-C_4)-alkylsulfonyl, and (C_1-C_5)-alkyl; and

X^- is a physiologically acceptable anion.

2. A compound according to claim 1, wherein R4 is a thiophene optionally substituted with one or several substituents independently selected from the group consisting of OH, SH, NO_2, CN, F, Cl, Br, I, $CONH_2$, COOH, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylsulfanyl, (C_1-C_4)-alkylsulfinyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkyl optionally substituted with one or several F or OH, and (C_1-C_4)-alkoxyl optionally substituted with one or several F.

3. A compound according to claim 1, wherein R4 is a phenyl optionally substituted with one or several substituents independently selected from the group consisting of OH, SH, NO_2, CN, F, Cl, Br, I, $CONH_2$, COOH, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylsulfanyl, (C_1-C_4)-alkylsulfinyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkyl optionally substituted with one or several F or OH, and (C_1-C_4)-alkoxyl optionally substituted with one or several F.

4. A compound according to any one of claims 1 to 3, wherein

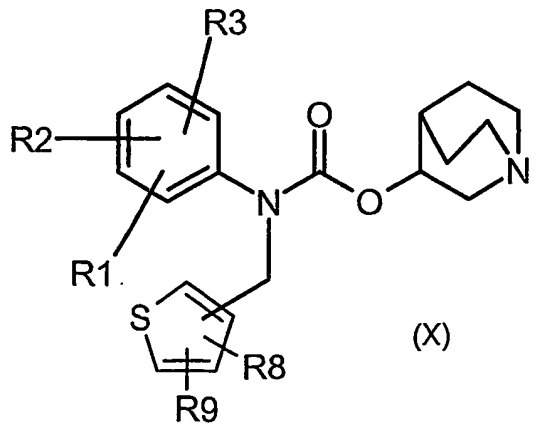
R5 is a (C_1-C_5)-alkyl substituted with one radical selected from the group consisting of R6, COR6, NR6R7, CONR6R7, NR7COR6, OR6, COOR6, OCOR6, SR6, SOR6, SO_2R6; and

R6 is a radical selected from the group consisting of:

a) phenyl optionally substituted with one or several substituents selected from the group consisting of OH, SH, CN, F, Cl, Br, I, $CONH_2$, COOH, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)alkylsulfanyl, (C_1-C_4)-alkylsulfinyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkyl optionally substituted with one or several F or OH, and (C_1-C_4)-alkoxyl optionally substituted with one or several F;

b) a *C*-linked radical of a five or six membered heterocyclic ring containing at least one heteroatom selected from the group consisting of O, S, and N, being this heterocyclic ring optionally substituted with one or several substituents independently selected from the group consisting of OH, SH, NO_2, CN, F, Cl, Br, I, $CONH_2$, COOH, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylsulfanyl, (C_1-C_4)-alkylsulfinyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkyl optionally substituted with one or several F or OH, and (C_1-C_4)-alkoxyl optionally substituted with one or several F.

5. Intermediate compound of formula (X)



(X)

and prodrugs, individual isomers, racemic or non-racemic mixtures of isomers, pharmaceutically acceptable salts, polymorphs and solvates thereof,
for the preparation of a compound of formula (I) as defined in claim 1, wherein R1, R2, R3, R8 and R9 are radicals independently selected from the group consisting of H, OH, NO_2, SH, CN, F, Cl, Br, I, $CONH_2$, COOH, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylsulfanyl, (C_1-C_4)-alkylsulfinyl, (C_1-C_4)-alkylsulfonyl, (C_1-C_4)-alkoxyl optionally substituted with one or several F, and (C_1-C_4)-alkyl optionally substituted with one or several F or OH, except when R8 and R9 are H; alternatively, either R1 and R2, or R2 and R3 may be forming a biradical selected from the group consisting of $-CH_2-CH_2-CH_2-$, and $-CH_2-CH_2-CH_2-CH_2-$.

6. A compound according to any one of claims 1 to 5, wherein the configuration of the 3 position in the quinuclidine ring is (*R*).

7. Use of a compound as defined in any one of claims 1 to 6, in the manufacture of a medicament for the treatment of urinary incontinence.

8. Use according to claim 7, wherein urinary incontinence is caused by overactive bladder.

9. Use of a compound as defined in any one of claims 1 to 6, in the manufacture of a medicament for the treatment of irritable bowel syndrome.

10. Use of a compound as defined in any one of claims 1 to 6, in the manufacture of a medicament for the treatment of respiratory diseases.

11. Use according to claim 10, wherein the disease is selected from the group consisting of chronic obstructive pulmonary disease, chronic bronchitis, asthma, emphysema, and rhinitis.

12. Use of a compound as defined in any one of claims 1 to 6, in the preparation of a medicament for ophthalmic interventions.

13. Pharmaceutical composition comprising a compound as defined in any one of claims 1 to 6 associated with other therapeutic agent selected from the group consisting of: calcium channel blockers, α-adrenoceptor antagonists, β_2-agonists, dopamine agonists, corticosteroids, phosphodiesterase IV inhibitors, leukotriene D4 antagonists, endothelin antagonists, substance-P antagonists, antitussives, decongestants, histamine H_1 antagonists, 5-lipooxygenase inhibitors, VLA-4 antagonists, and theophyline; and futher associated with pharmaceutically acceptable excipients.

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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

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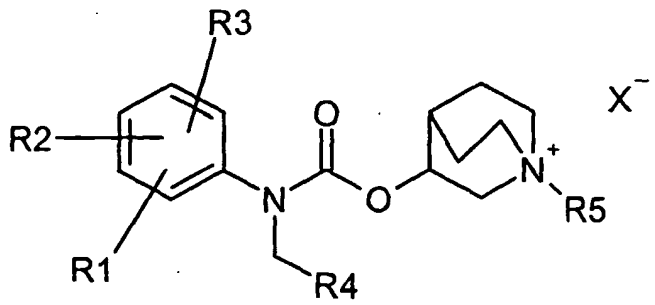
(54) Title: 1-ALKYL-1-AZONIABICYCLO'2.2.2!OCTANE CARBAMATE DERIVATIVES AND THEIR USE AS MUSCARINIC RECEPTOR ANTAGONISTS



(I)

(57) Abstract: Carbamate of general formula (I), wherein R1, R2 and R3 are H, OH, NO_2, SH, CN, F, Cl, Br, I, COOH, $CONH_2$, $(C_1$-$C_4)$-alkoxycarbonyl, (C_1C_4)-alkylsulfanyl, $(C_1$-$C_4)$-alkylsulfinyl, (C_1C_4)-alkylsulfonyl, $(C_1$-$C_4)$-alkoxyl optionally substituted with one or several F, and $(C_1$-$C_4)$-alkyl optionally substituted with one or several F or OH; R4 is cycloalkyl, phenyl, heteroaryl or a bicyclic ring system; R5 is cycloalkyl, $(C_5$-$C_{10})$-alkyl, a substituted $(C_1$-$C_{10})$-alkyl; and X^- is a physiologically acceptable anion. Carbamate (I) is selective M_3 receptor antagonists versus M_2 receptor and may be used for the treatment of urinary incontinence (particularly, the one caused by overactive bladder), irritable bowel syndrome, and respiratory disorders (particulary, chronic obstructive pulmonary disease, chronic bronchitis, asthma, emphysema, and rhinitis), as well as in ophthalmic interventions.

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02 051841 A (ALMIRALL PRODESFARMA S.A.) 4 July 2002 (2002-07-04) page 1; claim 2; examples 4,7,10-18,ETC.	1,6-9,13
A	EP 0 747 355 A (YAMANOUCHI PHARMACEUTICAL CO.,LTD.) 11 December 1996 (1996-12-11) cited in the application page 4, line 41 - line 55; claims	1
A	EP 0 801 067 A (YAMANOUCHI PHARMACEUTICAL CO.,LTD.) 15 October 1997 (1997-10-15) cited in the application page 3, line 5 - line 10; claims	1
A	WO 01 04118 A (ALLELIX BIOPHARMACEUTICALS INC.) 18 January 2001 (2001-01-18) cited in the application page 26, line 19 - line 21; claims	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Van Bijlen, H

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02051841 A	04-07-2002	WO 02051841 A1	04-07-2002
EP 747355 A	11-12-1996	AU 685225 B2	15-01-1998
		AU 1590995 A	29-08-1995
		EP 0747355 A1	11-12-1996
		CA 2182568 A1	17-08-1995
		CN 1140447 A	15-01-1997
		HU 76289 A2	28-07-1997
		WO 9521820 A1	17-08-1995
EP 801067 A	15-10-1997	AT 233761 T	15-03-2003
		AU 695616 B2	20-08-1998
		AU 4355396 A	19-07-1996
		DE 69529844 D1	10-04-2003
		DK 801067 T3	30-06-2003
		EP 0801067 A1	15-10-1997
		FI 972775 A	22-08-1997
		JP 3014457 B2	28-02-2000
		NO 973027 A	28-08-1997
		NZ 298144 A	27-04-1998
		PL 321019 A1	24-11-1997
		RU 2143432 C1	27-12-1999
		US 6017927 A	25-01-2000
		CA 2208839 A1	04-07-1996
		CN 1171109 A ,B	21-01-1998
		HU 77006 A2	02-03-1998
		WO 9620194 A1	04-07-1996
		US 6174896 B1	16-01-2001
WO 0104118 A	18-01-2001	ES 2165768 A1	16-03-2002
		AT 235492 T	15-04-2003
		AU 6433000 A	30-01-2001
		BG 106301 A	30-08-2002
		BR 0012434 A	02-04-2002
		CA 2381165 A1	18-01-2001
		CN 1373760 T	09-10-2002
		CZ 20020121 A3	13-11-2002
		DE 60001840 D1	30-04-2003
		DK 1200431 T3	21-07-2003
		EE 200200017 A	15-04-2003
		WO 0104118 A2	18-01-2001
		EP 1200431 A2	02-05-2002
		HU 0202100 A2	28-10-2002
		JP 2003504368 T	04-02-2003
		NO 20020180 A	13-03-2002
		SK 432002 A3	01-04-2003
		TR 200200768 T2	22-07-2002
		US 2003055080 A1	20-03-2003

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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

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(54) Title: 1-ALKYL-1-AZONIABICYCLO [2.2.2] OCTANE CARBAMATE DERIVATIVES AND THEIR USE AS MUSCARINIC RECEPTOR ANTAGONISTS

(57) Abstract: Carbamate of general formula (I), wherein R1, R2 and R3 are H, OH, NO_2, SH, CN, F, Cl, Br, I, COOH, $CONH_2$, (C_1-C_4)-alkoxycarbonyl, (C_1C_4)-alkylsulfanyl, (C_1-C_4)-alkylsulfinyl, (C_1C_4)-alkylsulfonyl, (C_1-C_4)-alkoxyl optionally substituted with one or several F, and (C_1-C_4)-alkyl optionally substituted with one or several F or OH; R4 is cycloalkyl, phenyl, heteroaryl or a bicyclic ring system; R5 is cycloalkyl, (C_5-C_{10})-alkyl, a substituted (C_1-C_{10})-alkyl; and X^- is a physiologically acceptable anion. Carbamate (I) is selective M_3 receptor antagonists versus M_2 receptor and may be used for the treatment of urinary incontinence (particularly, the one caused by overactive bladder), irritable bowel syndrome, and respiratory disorders (particulary, chronic obstructive pulmonary disease, chronic bronchitis, asthma, emphysema, and rhinitis), as well as in ophthalmic interventions.

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